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Archives of Internal Medicine

VOLUME 52 AUGUST, 1933 NUMBER 2

THERAPEUTIC EFFECT OF TOTAL ABLATION OF NORMAL THYROID ON CONGESTIVE HEART FAILURE AND ANGINA PECTORIS

III. EARLY RESULTS IN VARIOUS TYPES OF CARDIOVASCULAR DISEASE AND COINCIDENT PATHOLOGIC STATES WITHOUT CLINICAL OR PATHOLOGIC EVIDENCE OF THYROID TOXICITY

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This communication is a report on the therapeutic results of total ablation of the normal thyroid gland in a series of 10 patients with congestive heart failure or angina pectoris. Patient G. F. (case 11), on whom this procedure was first performed, was the subject of a previous report;[1] included here is an account of his subsequent clinical course.

The clinical observations which provided the rationale for this procedure began in 1924 with the development of an accurate method for measuring the velocity of the blood flow through the lungs.[2] Measure-

This study was aided by a grant from the William W. Wellington Memorial Research Fund of Harvard University.

From the Medical and Surgical Services and the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard University Medical School.

1. Blumgart, H. L.; Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **51**:866 (June) 1933.

2. (*a*) Blumgart, H. L., and Yens, O. C.: The Rate of Blood Flow as Determined by a New Method, Am. J. Physiol. **72**:1, 1925; (*b*) Studies on the Velocity of Blood Flow: I. The Method Utilized, J. Clin. Investigation **4**:1, 1927. (*c*) Blumgart, H. L., and Weiss, S.: The Velocity of Venous Blood to the Right Heart in Man, Proc. Soc. Exper. Biol. & Med. **23**:694, 1926; (*d*) Studies on the Velocity of Blood Flow: II. The Velocity of Blood Flow in Normal Resting Individuals, and a Critique of the Method Used, J. Clin. Investigation **4**:15, 1927;

(Footnote continued on page 166)

ments in more than 600 subjects demonstrated that, normally, the velocity of flow was directly determined by the metabolic demands of the body.[3] The metabolic demands of the body were gaged by the basal metabolic rate. When the metabolic rate was accelerated, as in thyrotoxicosis,[3d] the speed of blood flow was proportionately increased; on the other hand, when the metabolic rate was depressed, as in myxedema,[4] the blood velocity was correspondingly lowered. Patients with compensated heart disease were found to have a blood velocity within normal limits, in accord with the normal level of the basal metabolic rate. But in subjects with congestive heart failure, in spite of a normal metabolic rate, the blood velocity was considerably slowed. This lack of correspondence offered an explanation for the presence of the symptoms and signs of decompensation which were in proportion to the degree of slowing of the blood velocity.[5] The corollary of these observations was obvious: Since therapeutic attack directed toward the

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(*e*) VI. The Method of Collecting the Active Deposit of Radium and Its Preparation for Intravenous Injection, ibid. **4**:389, 1927; (*f*) VII. The Pulmonary Circulation Time in Normal Resting Individuals, ibid. **4**:399, 1927; (*g*) IX. The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardiovascular Disease, ibid. **5**:343, 1928.

3. (*a*) Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: III. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Rheumatic and Syphilitic Heart Disease, J. Clin. Investigation **4**:149, 1927; (*b*) IV. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Arteriosclerosis and in Patients with Arterial Hypertension, ibid. **4**:173, 1927; (*c*) footnote 2*f*; (*d*) Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: XIII. The Circulatory Response to Thyrotoxicosis, J. Clin. Investigation **9**:69, 1930.

4. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: XIV. The Circulation in Myxedema with a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis, J. Clin. Investigation **9**:91, 1930.

5. (*a*) Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: V. The Physiological and the Pathological Significance of the Velocity of Blood Flow, J. Clin. Investigation **4**:199, 1927; (*b*) X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, ibid. **5**:379, 1928; (*c*) XI. The Pulmonary Circulation Time, the Minute Volume Blood Flow Through the Lungs, and the Quantity of Blood in the Lungs, ibid. **6**:103, 1928; (*d*) Weiss, S., and Blumgart, H. L.: The Effect of the Digitalis Bodies on the Velocity of Blood Flow Through the Lungs and on Other Aspects of the Circulation: A Study of Normal Subjects and Patients with Cardiovascular Disease, ibid. **7**:11, 1929; (*e*) Studies on the Velocity of Blood Flow: VII. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Pulmonary Emphysema, ibid. **4**:555, 1927.

circulation in chronic heart failure is unavailing, the way to relieve the circulation is to decrease the load on it by lowering the basal metabolic rate, i. e., by thyroidectomy. Subtotal thyroidectomy produced only temporary improvement.[1] It was not long before it was realized that anything short of complete removal of every vestige of thyroid gland would not permanently lower the metabolic rate, and that to accomplish this it was necessary to perform total ablation of the thyroid. Equilibrium between the metabolic rate and the blood velocity thus effected was found to restore compensation.[1]

HISTORICAL RÉSUMÉ

Relation Between Metabolic Rate and Velocity of Blood Flow.—An adequate flow of blood to the tissues implies two things. In the first place, an adequate amount of blood must be expelled from the heart per unit of time. In the second place, this blood must be transported to the sites of utilization at an adequate speed. Because measurements of the cardiac output are technically difficult and are not applicable to patients with congestive failure, studies of the velocity of blood flow were undertaken.[6] Measurements of any such single aspect of the circulation give an inevitably incomplete picture of all the circulatory changes within the body. They afford, however, insight into the general pathologic physiology of the circulation. When this information is correlated with the clinical findings and measurements of other important characteristics of the circulation, a clearer understanding of the nature of circulatory insufficiency is made possible.[6]

After a study of the velocity of blood flow in patients with normal basal metabolic rates, the circulation in thyrotoxicosis was studied, for this condition seemed to offer an exceptional opportunity to observe the effects of an increased metabolic rate on the circulation uncomplicated by many extraneous factors. In such patients without clinical evidence of cardiovascular disease, the velocity of blood flow was strikingly increased.[3d] This finding was in accord with the results of Bock[7] and of others,[8] which indicated that the minute volume output of the heart

6. Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease: The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, Medicine **10**:1, 1931.

7. Bock, A. V., quoted by Means, J. H.: Circulatory Disturbances in Diseases of the Glands of Internal Secretion, Endocrinology **9**:192, 1925.

8. (*a*) Burwell, C. S.; Smith, W. C., and Neighbors, D. W.: The Output of the Heart in Thyrotoxicosis with a Report of a Case of Thyrotoxicosis Combined with Primary Pernicious Anemia, Am. J. M. Sc. **178**:157, 1929; (*b*) Liljestrand, G., and Stenström, N.: Clinical Studies on the Work of the Heart During Rest: I. Blood Flow and Blood Pressure in Exophthalmic Goiter, Acta med. Scandinav. **63**:99, 1925; (*c*) Means, J. H., and Newburgh, L. H.: Studies of the Blood Flow by the Method of Krogh and Lindhard, Tr. A. Am. Physicians **30**: 51, 1915.

in thyrotoxic patients at rest corresponded to that in normal persons doing light work. These findings indicated the strain under which the heart labored in persons with elevated metabolism, even when at rest, and explained the frequency of circulatory insufficiency in thyrotoxicosis. The extent of the increase in the velocity of blood flow through the lungs was closely related to the extent of increase in the basal metabolic rate. This relationship was present in every instance and indicated the degree to which the velocity of blood flow was necessarily increased to support the metabolic needs of the tissues.

Several patients with essential hypertension but without clinical evidence of thyrotoxicosis were also studied.[3d] In some of these patients the basal metabolic rate was elevated as high as plus 33 per cent. The increase in the velocity of blood flow through the lungs was similar to that observed in thyrotoxic patients with equally high metabolic rates but without hypertension. These findings were in accord with certain observations on the minute volume output of the heart.[9] It was felt that the increased velocity of blood flow through the lungs in these conditions was due to the elevated metabolism rather than to a specific toxic effect on the heart.[3d]

In patients with congestive failure, the speed of blood flow was slower than in comparable compensated persons with the same basal metabolic rate.[2g] Thyrotoxic patients with clinical evidence of cardiovascular disease were studied.[3d] These patients complained of dyspnea on the slightest exertion. In them, the velocity of blood flow, though faster than normal, was not so fast as that of patients with similarly elevated basal metabolic rates who showed no evidence of cardiovascular disease.

Patients with circulatory insufficiency and presumably a normal basal metabolic rate also showed a decided slowing in blood flow, even when early symptoms of circulatory insufficiency, such as palpitation on exertion, had occurred. With the appearance of more advanced signs of congestive failure, the retardation in the speed of blood became more pronounced and generally paralleled the degree of circulatory failure. It became apparent that circulatory insufficiency consists in the failure of the heart to maintain a blood supply adequate to the ordinary needs of the tissues at any given metabolic level.[6]

Of particular interest were the findings in patients with myxedema. In these patients a degree of slowing in the blood flow through the lungs was found, which corresponded closely with the degree to which the

9. Blalock, A., and Harrison, T. R.: The Effects of Thyroidectomy and Thyroid Feeding on the Cardiac Output, Surg., Gynec. & Obst. **44**:617, 1927. Davies, H. W.; Meakins, J., and Sands, J.: Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood: V. The Blood Gases and Circulation Rate in Hyperthyroidism, Heart **11**:299, 1924. Liljestrand and Stenström.[8b]

metabolic rate was lowered. The slowing of the blood flow in myxedema was not entirely unexpected, but the degree of slowing was striking, being almost as great as that observed in patients with rheumatic valvular heart disease and auricular fibrillation, who had previously suffered from severe circulatory decompensation and showed symptoms or signs of congestive failure at the time of the test.[4] None of the myxedematous patients, however, showed evidence of cardiovascular disease. The fact that the myxedematous patients showed no evidence of circulatory insufficiency with a speed of blood flow approximately the same as that of decompensated persons demonstrated the fact that the adequacy of a given speed of blood flow can be decided only in relation to the metabolic needs of the tissues.[4]

The thought therefore arose that if the normal metabolic rate of the patient with congestive failure were reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of his body. In terms of the law of supply and demand, the supply of blood in such a patient with congestive failure would not be increased, but the metabolic demands of his body would be decreased to a level in conformity with his blood supply.

These considerations in regard to congestive failure were equally applicable to angina pectoris.[10] The higher the metabolic rate, the greater are the output of the heart and the velocity of blood flow. The consequent increased work of the heart necessitates an increased coronary blood supply. Because of these considerations and because the intrinsic metabolic needs of the myocardium rise along with those of the rest of the body, the blood supply to the heart must be greater at normal metabolic rates than at the lower rate of myxedema. With arteriosclerotic narrowing of the coronary vessels, the blood supply of the heart through these vessels may be inadequate to the needs of a normal metabolic rate although sufficient for the needs of the heart at lower metabolic rates.

This analysis of the relation of the clinical manifestations of circulatory insufficiency to the metabolic needs of the tissues and the concept that a permanently lowered metabolism may be beneficial to patients with congestive failure or angina pectoris of nonthyrogenous origin were in accord with available knowledge in the literature.

Relation Between Thyrotoxicosis and Heart Disease.—Beginning with the earliest descriptions of thyrotoxicosis, numerous observers have

10. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: XV. The Velocity of Blood Flow and Other Aspects of the Circulation in Patients with "Primary" and Secondary Anemia and in Two Patients with Polycythemia Vera, J. Clin. Investigation **9**:679, 1931. Starling, E. H.: The Linacre Lecture on the Law of the Heart, New York, Longmans, Green & Co., 1918.

noted the frequent occurrence of congestive failure or of angina pectoris in this disease and improvement in the circulation with subsidence of thyroid activity. Parry's original account of exophthalmic goiter in 1825 appears at the beginning of the chapter entitled "Diseases of the Heart."[11] *"Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the heart. Case 1.* There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed, in that connection, by medical writers. The malady to which I allude is enlargement of the thyroid gland." In some patients, Parry noted the appearance of congestive failure or of angina pectoris with the development of the classic signs of exophthalmic goiter; in others, angina pectoris or palpitation and nervousness appeared several months before enlargement of the thyroid. Parry also clearly recorded subsidence of congestive failure with a decrease in the enlargement of the thyroid gland.

After the original accounts of the disease, practically all the signs and symptoms of the condition that are now known, according to Means,[12] were recognized and described by such masters as Trousseau,[13] Marie[14] and Charcot.[15] With the advent of operative treatment made possible by the work of Billroth[16] and the classic contributions of Kocher,[17] the effect of thyroidectomy on congestive failure was again clearly stated. In the extensive report of Kocher's cases by his son in 1902, the disappearance of congestive failure following thyroidectomy is described.[18] In the latter part of the nineteenth and the earlier years of the twentieth century, clinical interest was reawakened in various

11. Parry, C. H.: Collections from Unpublished Medical Writings, London, Underwoods, 1825, vol. 2.

12. Means, J. H., and Richardson, E. P.: The Diagnosis and Treatment of Diseases of the Thyroid, in Christian, H. A.: Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4.

13. Trousseau, A.: Lectures on Clinical Medicine, translated by P. V. Bazire, Philadelphia, Lindsay & Blakiston, 1867, vol. 1, p. 542.

14. Marie, P.: Sur la nature et sur quelques-uns des symptômes de la maladie de Basedow, Arch. de neurol. **6**:79, 1883.

15. Charcot, J. M.: Maladie de Basedow (goître exophthalmique); formes frustes; nouveau signe physique; traitement par l'électricité, Gaz. d. hôp. **58**:98 and 113, 1885.

16. Billroth, T.: Chirurgische Klinik, Zürich, 1860-1867, Berlin, A. Hirschwald, 1869. Wölfler, A.: Die Kropfextirpationen an Billroth's Klinik von 1877 bis 1881, Wien. med. Wchnschr. **32**:5, 1882.

17. Kocher, T.: Zur Pathologie und Therapie des Kropfes, Deutsche Ztschr. f. Chir. **10**:191, 1878; Ueber Kropfextirpation und ihre Folgen, Arch. f. klin. Chir. **29**:254, 1883.

18. Kocher, A.: Ueber Morbus Basedowi, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **1**:1, 1902.

types of thyrotoxicosis in which several or many of the characteristic features are absent, increasing reliance being placed on measurements of the basal metabolic rate and, since 1923, on the response to iodine therapy before operation.[19] Of particular interest were the careful studies of Hamilton,[20] begun in 1920, on the effect of subtotal thyroidectomy in 50 patients with signs of congestive heart failure due to hyperthyroidism. He concluded that "The response to treatment . . . is indeed unique." In 1931, Morris maintained that the basal metabolic rate in patients with thyrotoxicosis could be within normal limits. He described a group of cases of " 'thyroid heart' with low basal metabolic rate" in which, he stated, "the basal metabolic rate has been normal or subnormal; yet their response to subtotal thyroidectomy has differed in no way from that of patients with similar symptoms and increased metabolic rate." Morris concluded that "when evidence of a pre-existing thyrotoxic state is found, even with a subnormal basal metabolic rate, subtotal thyroidectomy may be indicated." [21] Recently Rosenblum and Levine reported the results of subtotal thyroidectomy in a group of patients with hyperthyroidism and significant heart disease.[22] They found immediate marked improvement which was extremely well maintained. One of this series of patients with hyperthyroidism and significant heart disease improved after the administration of compound solution of iodine. The removed portion of the gland appeared normal, leading the authors to infer that "the metabolism test, even when within normal limits, may not absolutely rule out active hyperthyroidism, or the finding of a normal gland may not mean that the gland has been

19. Minnich, W.: Das Kropfherz und die Beziehungen der Schilddrüsenerkrankungen zu dem Kreislaufapparat, Vienna, Franz Deuticke, 1904. Mobius, P. J.: Die Basedowische Krankheit, in Nothnagel: Encyclopedia of Practical Medicine, Philadelphia, 1896, vol. 22, p. 1. Romberg, Ernst: Lehrbuch der Krankheiten des Herzens und der Blutgefässe, Stuttgart, Ferdinand Enke, 1921. Dameshek, W.: The Heart in Hyperthyroidism, Boston M. & S. J. **190**:487, 1924. Lahey, F. H., and Hamilton, B. E.: Thyrocardiacs: Their Diagnostic Difficulties; Their Surgical Treatment, Surg., Gynec. & Obst. **39**:10, 1924. Kerr, W. J., and Hensel, G. C.: Observations of the Cardiovascular System in Thyroid Disease, Arch. Int. Med. **31**:398 (March) 1923. Plummer, H. S.: Results of Administering Iodin to Patients Having Exophthalmic Goiter, J. A. M. A. **80**: 1955 (June 30) 1923.

20. Hamilton, B. E.: Clinical Notes on Hearts in Hyperthyroidism, Boston M. & S. J. **186**:216, 1922; Heart Failure of the Congestive Type Caused by Hyperthyroidism, J. A. M. A. **83**:405 (Aug. 9) 1924.

21. Morris, R. S.: The "Thyroid Heart" with Low Basal Metabolic Rate, Am. J. M. Sc. **121**:297, 1931; Thyrotoxic Circulatory Symptoms with Low Metabolic Rate, Am. Heart J. **6**:730, 1931.

22. Rosenblum, H. H., and Levine, S. A.: What Happens Eventually to Patients with Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy? Am. J. M. Sc. **185**:219, 1933.

functioning normal. Finally, it is possible that partial removal of a normal gland may be helpful in patients who have either angina pectoris or the congestive type of heart failure." Several investigators have performed subtotal thyroidectomy on patients with no clinical thyrotoxicosis without producing clinical improvement or permanently lowering the metabolic rate. Rose,[22a] in 1932, discussed the difficulties in differential diagnosis between malignant hypertensive vascular disease and hyperthyroidism, even after prolonged observation of the patient. He noted that Riesman,[22b] in 1919, and Boas and Shapiro,[22c] in 1925 and 1926, had described hypertensive patients with loss of weight, tachycardia, diastolic hypertension, persistently elevated basal metabolism, nervousness and pigmentation of the skin but without definite thyrotoxicosis. Subtotal thyroidectomy in 3 of the cases was without effect. Rose reported a similar case in which "maximal subtotal thyroidectomy" was performed, a small amount of thyroid tissue being left at the upper pole of each lateral lobe. The gland appeared normal grossly and microscopically. The elevated basal metabolic rate and clinical course were unaffected, the patient dying in coma five months later. Rose concluded that "the result in this case certainly does not support our thought that thyroidectomy might favorably influence the course of malignant hypertension. However, we were not successful in producing any manifestations of hypothyroidism despite the amount of thyroid tissue removed. The persistent elevation of the basal metabolism and absence of thyreoprival symptoms after operation is noteworthy. It is conceivable that if a sufficient degree of hypothyroidism could be thus produced, cardiac overactivity might be reduced, the pulse rate decreased, and the arterial tension possibly lowered." Partial suprarenalectomy and subtotal thyroidectomy were performed on 2 patients with cardiovascular disease and 1 patient with arterial hypertension by Crile [23] without encouraging results. These patients were evidently in a state of "pathologic emotional or nervous excitation," but were not thyrotoxic. Crile hoped by such operations to minimize the "excessive uncontrolled activity or kinetic drive." These failures to observe improvement which would justify application of the procedure to other patients is understandable in the light of our own failures

22a. Rose, E.: Malignant Hypertensive Vascular Disease Simulating Hyperthyroidism: Clinical Course Following Maximal Subtotal Thyroidectomy, M. Clin. North America **16**:261, 1932.

22b. Riesman, D.: Hypertension in Women, J. A. M. A. **73**:330 (Aug. 2) 1919.

22c. Boas, E. P., and Shapiro, S.: Diastolic Hypertension with Increased Basal Metabolic Rate, J. A. M. A. **84**:1558 (May 23) 1925; Further Observations on Patients with Hypertension and Increased Basal Metabolic Rate, Am. Heart J. **1**: 643 (June) 1926.

23. Crile, G.: The Treatment of Certain Types of Hyperthyroidism, Tr. Am. A. Study Goiter **1**:1, 1932.

when subtotal thyroidectomy was performed, and illustrates the necessity of complete ablation of the thyroid gland.

The Effect of the Administration of Thyroid Substance to Patients with Myxedema.—The administration of thyroid substance to patients with myxedema is followed by a rise in the basal metabolic rate and a proportionate increase in the speed of blood flow.[4] This increased speed of blood flow denotes an increased amount of work on the part of the heart and serves to explain the observations showing that the administration of thyroid to such patients may precipitate angina pectoris or circulatory failure. These considerations were likewise in accord with the ideas underlying the proposed investigation.

PLAN OF INVESTIGATION AND METHODS

The course of chronic heart disease is often irregular and characterized by periods of unexpected exacerbation and remission. The fact that recovery from such remissions may be complete for varying periods made it imperative to select only patients in whom the course of the disease had been progressive and who showed evidence of incapacity even during a period of remission. The patients with congestive failure had all been treated by rest in bed for a long period, and although they may have been free from symptoms after prolonged rest in bed they regularly showed evidence of congestive failure on getting out of bed. The condition in each case was such that definite improvement could be confidently attributed to the operative procedure.

It was difficult to obtain patients who met with these requirements, for many who presented a history of progressive disease failed to give sufficient objective confirmation of their incapacity when carefully studied by exercise and other tests. For this reason, the situation in each case was appraised independently by several observers before a decision was reached. Patients with a history of angina pectoris were studied under standard conditions after exercise, and it was shown that a number of them did not have true angina pectoris.

It was imperative to select patients who were fair operative risks. Obviously, a patient was not a good risk at the height of an acute exacerbation with signs and symptoms of congestive failure. It was therefore necessary in some cases to wait for a period of improvement and to exert every effort to relieve such signs as edema, for example, by diuretics.

No patient was chosen whose prognosis for life was good. In each instance the operation was offered to the patient with a full account of its experimental status without minimizing the risk of operation. No better gage of the predicament of most of these patients could be found than their pathetic desire to hazard any of the dangers involved in order

to secure possible benefit after having suffered for many years and after having observed their condition become progressively worse in spite of medical treatment.

The patients selected had diverse types of cardiovascular disease, i. e., arteriosclerotic heart disease with congestive failure, arteriosclerotic heart disease with angina pectoris, arteriosclerotic heart disease with hypertension and paroxysmal dyspnea, cor pulmonale with right ventricular failure, and rheumatic valvular heart disease with normal rhythm or with auricular fibrillation. One of the patients, aged 66, had aortic insufficiency, and the serologic tests for syphilis were positive. He had suffered from dyspnea for many years, and it was felt that the primary cause of his symptoms and signs was cardiovascular arteriosclerosis.

Patients with circulatory failure due to syphilitic cardiovascular disease were not chosen for this study because of the rapid progression once the signs and symptoms of circulatory insufficiency appear.[24] Patients with active rheumatic infection, recent vascular accidents or the active phases of acute coronary thrombosis, and those unable to describe their symptoms clearly and accurately were not chosen. No symptoms or signs of thyrotoxicosis were present; no patient gave a history of preexisting thyrotoxicosis. Physical examination of the thyroid gave normal findings. Pathologically, the glands were normal, except in patient W. L. (case 7), whose thyroid showed quiescent colloid nodular goiter. We have not operated on patients who have not reached physical maturity. It may be possible, however, to obviate the danger of possible cretinism in such cases by administering small amounts of thyroid substances and at the same time to relieve some of the burden on the heart.

Detailed clinical study of the preoperative and postoperative condition of each patient was carried out independently by several observers. The patients were studied before operation for periods ranging from two weeks to several months. This was done not only to appraise the clinical condition as accurately as possible but also to improve the condition and so minimize the risk of operation. As we realize the inevitable importance of suggestion in any therapeutic procedure, we have attempted to evaluate the preoperative and postoperative condition of our patients by as many objective criteria as possible. Daily measurements of the blood pressure, the vital capacity of the lungs and the body weight were made under standardized conditions. Roentgenograms of the chest taken at a distance of 7 feet (213 cm.) were made several days before operation and were repeated once a month, or more

24. Scott, R. W.: Symptoms and Clinical Course of Syphilitic Aortic Insufficiency, Am. Heart J. **6**:86, 1930. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.

often if indicated. Electrocardiographic tracings in most cases were obtained at ten day intervals. Photographs were also taken before and after operation.

The basal metabolic rate was measured with a Collins Benedict-Roth apparatus. Sedatives were not given the night preceding the determination of the basal metabolism. Patients with orthopnea were allowed to lie in a semirecumbent position. On each occasion measurements were made in duplicate or triplicate. Measurements were repeated frequently before operation until it was evident that the patient was under truly basal conditions and until successive tests on different days agreed within 5 per cent. The basal metabolic rate was again estimated after operation, as soon as the patient's condition allowed, and was repeated at approximately weekly intervals. The Aub-Du Bois normal standards were used.[25]

The venous pressure was measured by the direct venipuncture method of Moritz and Tabora.[26] When possible, the readings were obtained with the patient recumbent, the right auricle being assumed to be 5 cm. below the level of the fourth costochondral junction. When orthopneic, the patient was allowed to sit up at an angle of 45 degrees, the right auricle then being assumed to be 2.5 cm. below the fourth costochondral junction. The accuracy of these assumptions has been checked by measurements of the venous pressure in the same patient in both positions.

The arm to tongue circulation time was used as an index of the velocity of blood flow, according to the method of Winternitz, Deutsch and Brüll.[27] From 3 to 5 cc. of sodium dehydrocholate (decholin) was injected into an antecubital vein, and the time of arrival in the tongue was estimated by a signal from the patient when he experienced a bitter taste in the mouth.[27a] The results by this method were found to conform satisfactorily with measurements of the "arm to arm circulation time" and "crude pulmonary circulation time" of previous studies by the radioactive method. A number 18 or 16 gage needle was used in order to shorten the time of injection and to facilitate a sharp end-point of detection in the presence of marked slowing in the blood flow. Measurements of the velocity of blood flow were made in triplicate at the same

25. Aub, J. C., and Du Bois, E. F.: Clinical Calorimetry: XIX. The Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (May, pt. 2) 1917.

26. Moritz, F., and Tabora, D. V.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu Bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

27. Winternitz, M.; Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, Med. Klin. **27**:986, 1931.

27a. The ampules of decholin were supplied by Mr. Paul de Haen of Riedel-de Haen, Inc.

venipuncture and were accepted only when at least two determinations checked within two seconds. The circulation time was usually estimated in conjunction with the measurements of the venous pressure. Before operation the tests were carried out and checked on at least two different days. After operation the circulation time and the venous pressure were determined at approximately weekly intervals. The average normal arm to tongue circulation time by the decholin method is eighteen seconds.[28]

In addition to the usual laboratory examination of the blood, the level of various substances in the blood serum during fasting was measured before and at varying intervals after operation. The substances measured included nonprotein nitrogen, sugar, inorganic phosphate, calcium, cholesterol, total protein, albumin, globulin, carbon dioxide content and the icteric index. The blood was obtained from an antecubital vein with minimum stasis, and was collected and centrifugated under oil.

The simple exercise tolerance tests for patients with congestive failure were found not entirely satisfactory because of the degree of disability shown by our subjects. Master and Oppenheimer [29] gaged the degree of cardiac disability by determining the maximum amount of work which patients could perform in one and one-half minutes and still have the pulse and blood pressure return to the resting level within two minutes after the completion of the exercise. The work consisted in repeatedly climbing a staircase of 2 steps, each being 9 inches (22.9 cm.) high. They presented, for comparison, tables indicating the amount of work which normal persons could perform under similar conditions. This test offers the advantage of simplicity and freedom from the necessity of training. Its disadvantage lies in the ease of fatigability of cardiac patients, making it impossible to repeat the test at frequent intervals.

In the test as performed by us the patient remained seated until the pulse and blood pressure became stationary. He then performed the amount of work specified in the tables of Master and Oppenheimer for normal persons of the same age, weight, sex and height. An attempt was made to have the patient perform the necessary number of trips within one and a half minutes, following which he immediately returned to his chair. The pulse rate and blood pressure were recorded at intervals of one-half minute until they returned to their original resting level.

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28. Gargill, S. L.: The Use of Decholin as a Clinical Test of the Velocity of Blood Flow, New England J. Med., to be published.

29. Master, A. M., and Oppenheimer, E. T.: A Simple Exercise Tolerance Test for Circulatory Efficiency with Standard Tables for Normal Individuals, Am. J. M. Sc. **177**:223, 1929.

The following observations were made: (1) the degree of facility displayed by the patient and the length of time necessary to perform the amount of work prescribed; (2) the degree of fatigue produced; (3) the pulse rate during rest and the pulse curve following exercise; (4) the blood pressure level at rest and the blood pressure curve following exercise; (5) the degree and duration of dyspnea, cyanosis and other signs of circulatory embarrassment following work.

The exercise tolerance test was performed on two separate days before operation, a few days after the patient had been allowed to walk for the first time after operation and subsequently at approximately weekly intervals throughout the patient's stay in the hospital. In a patient with angina pectoris, the condition was evaluated objectively by measuring the type and amount of exercise necessary to precipitate an attack under accurately controlled conditions. A more detailed description of this test will be found in the history of the case.

REPORT OF CASES

CASE 1.—*Rheumatic heart disease, mitral stenosis and insufficiency, dyspnea and hemoptysis for seven years; attacks of congestive failure for five years.*

E. W., a man, aged 27, an unskilled worker, was transferred to the Beth Israel Hospital on March 8, 1933, through the kindness of Dr. Roger D. Mackey, Lieutenant Commander, Medical Corps, United States Navy. He complained of progressive shortness of breath and repeated hemoptysis of seven years' duration. He had rheumatic fever at the age of 6, with yearly recurrences for four years and a final attack in 1926 at the age of 20. The present illness began in 1926, seven years before admission, when he noticed that he tired easily and frequently coughed up small amounts of blood. During the next two years these symptoms increased, hemoptysis amounting to one or two wine glasses full and occurring every three or four weeks. He was finally forced to bed in 1928 for two and a half weeks. After this he returned to work, in spite of dyspnea, orthopnea and marked palpitation. Hemoptysis increased to approximately one-half cupful and occurred two or three times a week. In 1930 he was forced to leave his job although he was working but very little. Orthopnea and dyspnea became marked. Attacks of sharp intermittent pains appeared substernally, posteriorly between the shoulder blades and in both axillae. The pains lasted from two to three hours, were usually precipitated by movement, particularly after getting into bed, and were relieved somewhat by rest.

During the next two years, from 1930 to 1932, the patient spent several weeks in bed at home and in several hospitals. In 1932 he entered a hospital in Maine with generalized anasarca. He remained there for seven months, hemoptysis occurring almost daily, interrupted by occasional periods of freedom from this symptom, the longest period being two weeks. In February, 1933, he was admitted to a hospital near Boston, apparently moribund and suffering from congestive failure with general anasarca, hemoptysis and intense respiratory distress. After five weeks of complete rest in bed he was transferred to the Beth Israel Hospital.

Physical examination shortly after he came under our supervision revealed a well developed, alert young man, propped up in bed, moderately dyspneic, with slight cyanosis of the lips and malar prominences. The apex impulse was diffuse in the sixth interspace, 12.5 cm. to the left of the midsternal line. The cardiac

rhythm was regular; the rate was 100 per minute. The first sound at the apex and the second pulmonic sound were accentuated. At the mitral area there were a systolic blow and a diastolic rumbling murmur. The blood pressure was 110 systolic and 60 diastolic. At the base of the left lung there were dulness, diminished vocal fremitus and medium crepitant râles. The lungs were otherwise clear. In the right upper quadrant of the abdomen there were increased resistance and tenderness, although a definite edge of the liver was not felt. The fingers showed slight clubbing.

Studies of the urine and blood gave normal findings. A roentgenogram of the chest taken at a distance of 7 feet showed the transverse diameter of the heart to be 17.3 cm., and the internal diameter of the chest, 31.8 cm.; there was marked prominence in the region of the auricles. The pulmonary markings were considerably increased, and the bases of both lungs showed diminished radiance consistent with pulmonic fibrosis of cardiac origin. Electrocardiographic tracings showed normal sinus rhythm, a P R interval of 0.22 seconds and right axis deviation. Repeated measurements showed variations in venous pressure from 4.4 to 12.3 cm. of water. The velocity of blood flow by the decholin method ranged from twenty-one to twenty-four seconds. The basal metabolic rates, determined on two successive occasions, were plus 4 and plus 7 per cent, respectively. Exercise tolerance tests were performed to gage the extent of the patient's disability.

On March 17, total ablation of the thyroid gland was performed with the patient under gas-oxygen anesthesia.[30] Pathologic examination showed a normal gland. The patient's condition remained good throughout the operation; the ventricular rate rose from 104 to 135, the blood pressure, to 135 systolic and 70 diastolic; they remained at these levels to the end of the operation, which required one hour and fifty-six minutes. Approximately ten minutes later the patient opened his eyes and was able to talk. The temperature rose to 103 F. after operation and subsided to normal on the fourth day. The respiratory rate, which had shown daily rises to 30 per minute for the nine days preceding operation, rose to 35 immediately after operation, fell to 20 on the third day and continued at this level throughout the patient's stay in the hospital.

On the third postoperative day the patient stated that he felt better than he had just prior to operation. He noticed that he could turn from one side to the other without palpitation. Before operation palpitation occurred with a slight change of position in bed. His breathing was considerably easier, and there was a decrease in the respiratory rate.

The following routine notes were made by the resident physician:

March 28 (eleven days after operation): The patient is breathing decidedly easier, and he is free from palpitation.

April 4: The patient is now up and about, walking around and feeling definitely improved. He states that he breathes more easily and does not feel precordial distress and palpitation.

April 11: The patient continues to show steady and well marked improvement. He is up and about, walking around without any signs of discomfort.

April 14: The patient has gradually increased his activities so that he has been up and about the entire day for the past four days without any period of rest in bed except at night. The lungs show no râles, and the resistance and tenderness in the right upper quadrant have disappeared.

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30. This operation, as well as all others reported in this series, was performed by Dr. David D. Berlin.

Chart 1 shows the changes in the basal metabolic rate and the velocity of blood flow. Striking variations did not occur until the twenty-third day after operation, when the basal metabolic rate fell to minus 19 per cent. The velocity of blood flow, which was slightly prolonged to start with, became markedly prolonged at the time of the fall in the basal metabolic rate. Clinical improvement appeared to antedate slightly the fall in the basal metabolic rate and the prolongation of the circulation time, but the most striking improvement did not occur until later.

The patient stated that for the first time in seven years he was entirely free from the sensation of heaviness and pain in the left anterior part of the chest, a condition he had so long taken for granted that he had hardly commented on it before operation. He could sleep soundly lying perfectly flat in bed and was unaware of his heart action for the first time in five or more years.

A measured amount of exercise before operation resulted in considerable dyspnea and fatigue and a fall in blood pressure accompanied by almost a state

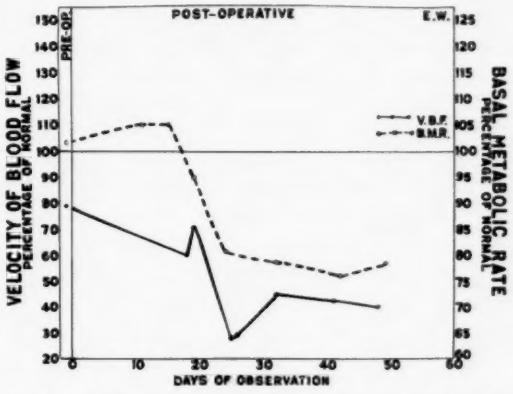

Chart 1 (case 1).—The relation between the velocity of blood flow and the basal metabolic rate.

of collapse. Test performances two weeks after operation showed appreciable improvement. The patient was able to perform the test with greater ease and facility and was less dyspneic and fatigued and the blood pressure rose during the exercise. A test performed seven weeks after operation demonstrated that the patient could do at least 60 per cent more work than was previously possible. Following this exercise the pulse and blood pressure returned to the resting level more rapidly than it had in the less severe preoperative test.

The patient continued to improve and has been up and about, climbing stairs and doing odd jobs, during the last five weeks without dyspnea or palpitation. On two occasions, a few days after thyroidectomy he coughed up small amounts of blood, but except for this he has had no cough or hemoptysis at any time, although before operation this was practically a daily occurrence. The red blood count rose from an average of 4,050,000 to 4,470,000 on the twenty-seventh day after operation, the hemoglobin rising from 55 to 63 per cent (Sahli). The vital capacity, which was relatively high to start with, remained at a level of approximately 3,500 cc. A roentgenogram taken at a distance of 7 feet one month after operation showed no change in the size of the heart. The electrocardiogram

showed an appreciable diminution in the voltage of the Q R S complex and a slight decrease in the height of the T waves.

The only evidence of clinical myxedema consists of a very slight yellowish pallor of the skin, and a slowing in the growth of hair. The patient was quick, responsive, systematic in work and capable of concentrating in a most satisfactory manner.

The patient was discharged on May 6. He left for his residence in New Hampshire and returned on May 23 for a follow-up examination. During the seventeen days of absence he carried on moderate activity, walking without stopping on an average of 1 mile daily. At no time did he show evidence of dyspnea. He slept well, and at no time had there been palpitation or hemoptysis. The vital capacity was 3,500 cc.

Comment.—This patient gave a history of repeated attacks of congestive failure since 1928, with cardiac invalidism since July, 1930. After operation conspicuous improvement was shown by the disappearance of palpitation, pain in the chest and hemoptysis. Breathing became easier and orthopnea disappeared, and he was able to perform more physical exercise with less discomfort. Paralleling the clinical improvement the basal metabolic rate became persistently lowered and the velocity of blood flow markedly prolonged. At the time of writing, four months after operation and after three months of moderate activity, the patient showed no evidence of congestive failure. Daily walks of 1 mile or more did not result in dyspnea. Hemoptysis, which was present daily before operation, no longer occurred, and he was restored from a state of physical incapacity to one of occupational usefulness.

Case 2.—*Rheumatic heart disease, mitral stenosis, aortic insufficiency, extreme cardiac enlargement, auricular fibrillation, pulmonary and renal infarction and attacks of congestive failure for twelve years.*

R. D., a man, 22 years of age, was admitted to the Beth Israel Hospital on March 16, 1933, with a history of shortness of breath of twelve years' duration. He had rheumatic fever at the age of 2, and in 1921, at the age of 10, was admitted to the Children's Hospital in Boston because of active rheumatic heart disease and congestive failure. Two years later he became very short of breath and was admitted to the Massachusetts General Hospital. During the next seven years, from 1922 to 1929, he suffered from shortness of breath, orthopnea, substernal pain, palpitation and edema of the legs, and was admitted four times to the Massachusetts Homeopathic Hospital. At times he was able to be up and do light work, but beginning in 1929 there was a rapid progression of symptoms with frequent attacks of hemoptysis, pain in the anterior part of the chest and palpitation, necessitating almost continuous rest in bed. In June, 1932, he had repeated attacks of massive hemoptysis with dyspnea, cyanosis and prostration, suggestive of pulmonic infarction. During one attack he was sent to the Somerville Hospital, and shortly afterward was transferred to a hospital for chronic diseases. Hemoptysis occurred frequently. In January, 1933, he had an attack of hematuria which persisted for three weeks. During the last six months he had several peculiar fainting spells suggestive of atypical epileptiform seizures. He was practically completely incapacitated, and sat up for only a short period each day.

Physical examination on admission revealed an unusually tall, well developed but undernourished, slightly dyspneic young man, propped up in bed. At the apex a thrill was palpable, and the impulse was diffuse in the sixth interspace 15 cm. to the left of the midsternal line. The sounds were absolutely irregular, the apical rate being 80. The first sound was markedly accentuated. In the mitral area a blowing systolic murmur and a rough diastolic murmur were heard. A diastolic murmur heard at the aortic area was transmitted downward along the left border of the sternum. Râles were heard at the bases of both lungs. The blood pressure was 120 systolic and 80 diastolic. The liver was not palpable. There was no edema.

Examination of the urine and blood gave normal results. A roentgenogram of the chest taken at a distance of 7 feet showed a transverse cardiac diameter of 20 cm. and an internal diameter of the chest of 32 cm. The heart was tremendously enlarged in all directions. Electrocardiographic tracings showed auricular fibrillation, a ventricular rate of 70, a diphasic T wave in lead I and slight right axis deviation. The venous pressure was 10 cm. of water. The vital capacity of the lungs ranged from 2,900 to 3,100 cc. The velocity of blood flow (arm to tongue time) varied from forty-two to forty-five seconds. The basal metabolic rate varied from minus 1 to minus 5 per cent.

On March 25, total ablation of the normal thyroid gland was performed with the patient under gas-oxygen anesthesia; the operation required two hours and nineteen minutes. The patient did well throughout. The blood pressure rose gradually from 110 to 140 systolic. The apex rate did not rise above 105, and the respiratory rate remained at 25 per minute during the operation. The temperature rose to 100 F. on the second postoperative day and reached normal on the fifth postoperative day. The pulse and respiration showed very little elevation.

On the second day after operation the patient volunteered that the constant pressure pain in the region of the heart which had been practically continuous for twelve years had disappeared. One week later he stated that his breathing was distinctly easier, that he could breathe more normally and that the pounding of his heart which always had been present with every change in position had disappeared. He appeared alert and happy. On the tenth day he was up and about for several hours, and his only complaint was that he was not permitted more activity. On the eleventh day he contracted a slight infection of the upper respiratory tract, and this was followed shortly by one of the atypical epileptiform seizures. On the twenty-second day after operation he stated that he felt clearer mentally than he had before operation. He again noted that his breathing was considerably better and that he could walk up and down the corridor without any appreciable shortness of breath or fatigue. Critical objective study appeared to corroborate his statements.

On April 19, twenty-five days after operation, he suddenly experienced pain in the chest; examination disclosed râles confined to the base of the left lung. Respiratory distress with profuse perspiration followed, and he coughed up large amounts of blood-tinged frothy sputum. A roentgenogram of the chest showed a definitely increased density over the left lung, somewhat more marked in the region of the upper lobe. The history of similar attacks in the past, the knowledge that he had fibrillation, the character of the onset and the physical findings strongly suggested the occurrence of pulmonary infarction.

Recovery from this attack was complete, but in the course of the next two weeks two other short attacks characterized by sudden dyspnea and the coughing up of pinkish froth occurred. These attacks lasted only a few minutes, and there was no recurrence. The patient continued to show the same improvement

evident soon after operation, remaining free from pain in the chest and palpitation. There was no orthopnea, and he was out of bed for short periods each day without dyspnea.

Chart 2 shows the changes in the basal metabolic rate and the velocity of blood flow. The metabolism fell rapidly, reaching minus 37 per cent on the fortieth day after operation. The arm to tongue circulation time, which was prolonged before operation, showed further slowing with the marked decrease in the metabolism. At the time when the basal metabolism had fallen to minus 37 per cent, the patient showed some drowsiness which was difficult to evaluate and may have been due to the hypothyroid state. For this reason, thyroid extract was administered. The effect is noted on the chart as a sharp rise in the basal metabolic rate.

Exercise tests showed striking improvement. Before operation, a given amount of exercise resulted in dyspnea, fatigue and a rise in the cardiac rate from 94 to 172 and from 90 to 160 per minute, with pulse deficits of from 70

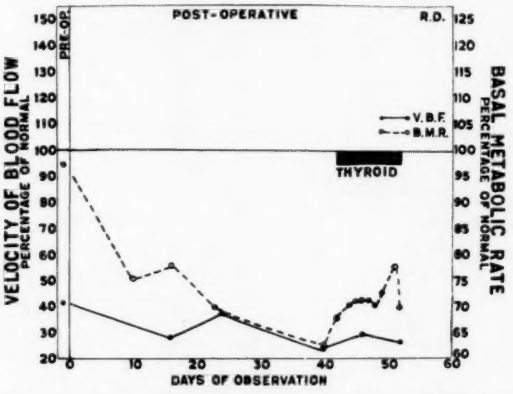

Chart 2 (case 2).—The relation between the velocity of blood flow and the basal metabolic rate.

to 80 per minute. The same performance after operation was carried out with considerably more ease, less dyspnea and no evident fatigue. The rise in the apical rate was from 72 to 148 per minute and from 68 to 80 per minute. Of added interest is the fact that the blood pressure during exercise showed an initial fall before operation in contrast to a definite rise in the performance after thyroidectomy.

Successive electrocardiograms showed a decrease in the voltage of the Q R S complexes from 14 to 8 millivolts. The T waves were not significantly changed. Before operation, the red cell count was 4,640,000; after operation, it rose slightly in spite of an appreciable loss of blood incurred by venesection during the attack of pulmonary edema. The preoperative pulse rate of from 70 to 90 gradually became slowed to 60 and later remained between 50 and 60 during convalescence. The blood pressure remained fairly constant at a level of 120 systolic and 70 diastolic. The vital capacity showed a definite increase immediately after operation to 12 per cent above the preoperative capacity, which ranged from 2,800 to 3,100 cc. Following the attack of pulmonary edema, however, it became diminished but was still somewhat elevated above the preoperative level.

Comment.—This patient, a man 22 years of age, with rheumatic heart disease, mitral stenosis and extreme cardiac enlargement gave a history of numerous attacks of congestive failure during the course of the past twelve years. He had attacks of massive hemoptysis suggestive of pulmonary infarction, and shortly before admission hematuria consistent with renal infarction. Ever since he could remember he had been conscious of pain in the region of the heart. After operation he showed significant improvement. Pain in the chest, palpitation and orthopnea disappeared. His response to exercise was attended with considerably less shortness of breath than was manifest in the tests before operation. At the time of writing, four months after operation, the basal metabolic rate remained persistently lowered, the velocity of blood flow was correspondingly prolonged, and the patient continued to show clinical improvement.

CASE 3.—*Syphilis, arteriosclerotic heart disease and congestive failure for six years.*

C. C., a man, aged 66, entered the Beth Israel Hospital on March 16, 1933. The family and past histories were irrelevant. He lived an active and vigorous life until the onset of his present illness.

In November, 1926, about six and a half years before entry, he contracted a cold in the head and a nonproductive cough which, while not very severe, failed to respond to treatment. At about the same time he was troubled by a feeling of "tightness in the chest" particularly at night, and noted the onset of shortness of breath, violent palpitation and marked weakness on slight exertion. His legs became swollen, and he was forced to stop work. After the administration of digitalis and rest in bed his condition improved. On returning to work six years before admission, the foregoing signs and symptoms recurred. During the next four years he was forced to spend much of his time in bed. His discomfort gradually increased; he became dyspneic while at rest and had to sleep propped up in bed. About two years before admission (February, 1931) he fainted on the street and was taken to the Boston City Hospital, where he remained for five weeks. Because of complete incapacitation he was transferred to a hospital for chronic diseases, where he remained until admission to the Beth Israel Hospital.

During the two years' stay at the State Infirmary he had repeated attacks of dyspnea, orthopnea, cyanosis, edema of the legs, loss of appetite and slight elevation of temperature, which came on about once every two months and lasted for a week. Between attacks he was quite comfortable, provided he remained in bed or in a chair.

Physical examination showed a well developed and moderately well nourished man. The retinal and peripheral vessels showed advanced arteriosclerosis. The apex impulse was seen and felt in the sixth interspace in the anterior axillary line. There were no thrills. The rhythm was regular except for many premature beats. A loud systolic murmur and a short diastolic murmur were heard in the mitral area, and a systolic murmur in the aortic area. The lungs were clear. There was no hepatic enlargement or peripheral edema. The blood pressure ranged from 130 systolic and 60 diastolic to 110 systolic and 70 diastolic. The vital capacity of the lungs varied from 2,700 to 3,300 cc. The weight was 134 pounds (60.8 Kg.).

The usual laboratory tests of the urine showed no abnormalities. The Wassermann, Kahn and Hinton tests of the blood were positive for syphilis. A roentgenogram of the heart taken at a distance of 7 feet showed moderate enlargement. There was marked calcification in the walls of the aorta. The electrocardiographic tracing showed normal sinus rhythm, auricular and ventricular premature beats, inverted T_1, spreading of the Q R S complex to 0.12 second and left axis deviation. The venous pressure varied from 3 to 5 cm. of water, and the arm to tongue circulation time, from thirty-two to thirty-six seconds. The metabolic rate was plus 10 per cent repeatedly.

On March 23, 1933, total ablation of a normal thyroid gland was performed with the patient under gas-oxygen anesthesia. The course after operation was smooth and uneventful. The temperature showed no rise. The ventricular rate increased from 60 to 80 beats per minute for three days, and the respirations continued at 20. The pathologist reported the gland to be normal.

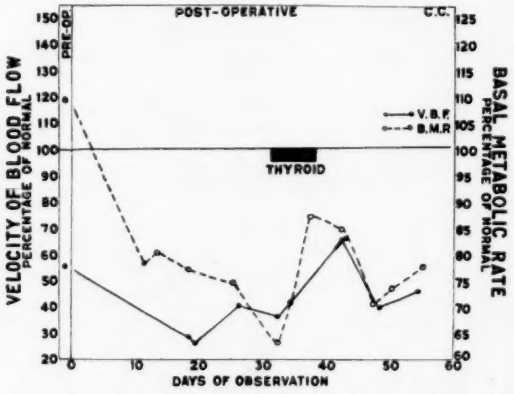

Chart 3 (case 3).—The relation between the velocity of blood flow and the basal metabolic rate.

On the fifth day after operation there was a noticeable change in the patient. He became more cheerful and buoyant and volunteered the information that he felt "ironed out." His palpitation had disappeared, he felt less short of breath, and, for the first time in years, could lie flat without discomfort or difficulty in breathing. Pounding in his chest had been present for so long that he had unconsciously learned to ignore it, and it was only with its disappearance that he realized how continuous it had been and how uncomfortable it had made him.

He was allowed to increase his activity gradually. On the twenty-second day after operation, after having been up and about the ward for about three hours a day during the preceding week, he showed no signs of decompensation. His appetite improved so that the hospital diet had to be increased. In thirty days he gained 10 pounds (4.5 Kg.) without showing any demonstrable edema. The heart rate remained about 60 beats per minute. The vital capacity increased from 600 to 1,200 cc. above the preoperative level. The blood pressure showed very little change, remaining approximately 120 systolic and 70 diastolic. The electrocardiographic tracing no longer revealed premature beats of auricular origin, although ventricular premature beats were still present. There was no significant

change in the height of the T waves or in the voltage of the Q R S complexes. Exercise tolerance tests showed a definite improvement compared to the response before operation in that dyspnea was less and the pulse and blood pressure returned to normal in a shorter time. Slight pallor and definite anemia developed after operation, the red count being 5,000,000 before operation and dropping to 4,180,000 and 3,890,000 on the nineteenth and thirty-second days after operation. Chart 3 shows the changes in the basal metabolic rate and the velocity of blood flow. The basal metabolic rate dropped rapidly, reaching minus 37 per cent on the thirty-third day after operation. The velocity of blood flow, which had been retarded as a consequence of cardiac insufficiency, became more prolonged as an adjustment to the diminished basal metabolic rate.

About the thirty-third day after operation the patient became increasingly drowsy, weak, apathetic and slow mentally. His skin was dry, and his appetite became poor. The vital capacity fell to the preoperative level. The blood cholesterol increased from its previous level of from 154 to 147 to 207 mg. per hundred cubic centimeters. Electrocardiographic tracings and roentgen measurement of the heart showed no significant changes. Râles appeared at the bases of both lungs, but there were no signs of peripheral edema. The patient had insomnia since the onset of his illness and had been receiving daily doses of barbital. The sudden onset of drowsiness was therefore considered as probably due to barbital poisoning, but since the basal metabolism had fallen to minus 37 per cent, myxedema as a cause could not be ruled out. Therefore, all sedatives were omitted, and 3 grains (0.195 Gm.) of thyroid extract was given daily for seven days. The basal metabolic rate rose to minus 13 per cent, and the velocity of blood flow increased strikingly. Premature auricular beats reappeared. The patient regained his former alertness and vitality, slept soundly at night and after a short rest in bed was able to walk without dyspnea or any evidence of congestive failure. He stated that he had not felt so well at any time during the preceding six years.

Comment.—This patient, a man aged 66, with a history of congestive failure of six years' duration and laboratory evidence of syphilis, showed striking improvement following total thyroidectomy. Palpitation, orthopnea and dyspnea disappeared, and the ability to perform exercise was definitely improved. At the time of writing, four months after operation, he was able to be up and about without dyspnea or edema. The vital capacity increased 600 to 1,200 cc. above the level before operation, and clinical improvement was paralleled by a decrease in the metabolic rate and a slowing of the velocity of blood flow.

CASE 4.—*Paget's disease, arteriosclerotic heart disease with hypertension, angina pectoris, cardiac asthma and congestive failure for two years.*

W. B., a man, aged 55, a shoe designer, was admitted to the Beth Israel Hospital on March 16, 1933. The past history was unimportant except for a gradual change in the shape of the long bones during the previous eighteen years. The present illness began in January, 1931, with recurring attacks of bronchitis. In March, he was suddenly awakened at night by a paroxysm of dyspnea which lasted twenty minutes. On attempting to lie flat attacks recurred and he became orthopneic; he was therefore removed to a hospital where he was digitalized and kept at complete rest in bed for five weeks. On discharge orthopnea and dyspnea on exertion persisted and increased in severity, forcing him again to enter a hospital, where he remained for six weeks. He felt somewhat better but a few weeks

later noted the onset of attacks of severe substernal pain, which were relieved within a few minutes by rest. Such attacks occurred about every two weeks. In July, he suddenly became dizzy and was removed to a hospital, where he remained for six weeks. Following discharge he experienced dyspnea and substernal pain on slight exertion, and for the first time he noted swelling of his ankles. On one occasion he was seized with an unusually severe attack of crushing substernal pain which radiated to the inner aspect of his left arm; the pain persisted for several minutes and was accompanied by marked dyspnea and weakness. In September, he was taken to the Boston City Hospital where the diagnosis of cardiac asthma was made. During this admission he had one attack of unconsciousness during which he became pulseless and was not expected to live. Because of his helpless physical condition he was transferred to a hospital for chronic disease. While there he was confined to bed and a wheel chair for several months and was fairly comfortable when so restricted. However, each time he tried to walk or to remain on his feet for even a brief part of the day marked dyspnea and edema of the ankles appeared. From the institution where he had been for sixteen months he was transferred to the Beth Israel Hospital.

Physical examination revealed a poorly nourished, middle-aged man with the general appearance of Paget's disease. The retinal vessels showed evidence of sclerosis. The heart was moderately enlarged, the apex impulse being in the fifth space 12 cm. from the midsternal line. The cardiac action was slow and regular. There was a systolic murmur at the apex. The lungs were clear. The liver was not palpable. The blood pressure was 180 systolic and 90 diastolic. The long bones of the legs, forearms and thighs showed anterior and lateral bowing. There was no edema.

Examination of the urine and blood gave normal findings. A roentgenogram taken at a distance of 7 feet showed the heart enlarged transversely and to the left, the cardiac diameter being 13.6 cm. and the internal diameter of the chest, 24.8 cm. An electrocardiogram showed normal sinus rhythm, the rate being 80. The T waves were inverted in leads II and III. Roentgenograms of the skull and the long bones showed changes typical of Paget's disease. The venous pressure varied from 3 to 6 cm. of water. The arm to tongue circulation time varied from seventeen to twenty-one seconds. The basal metabolic rate varied from plus 7 to plus 12 per cent. The vital capacity of the lungs ranged from 2,100 to 2,700 cc.

On March 24, 1933, total ablation of the normal thyroid gland was performed with the patient under gas-oxygen anesthesia. The operation was uneventful and required one hour and forty minutes. The blood pressure remained at the preoperative level of 180 systolic and 90 diastolic, the pulse rate not rising above 85. Within a few minutes after the operation the patient was able to talk. The temperature rose to 101 F. on the second day and reached normal on the fifth postoperative day. The pulse showed no elevation above 90.

One week after operation the patient stated that he felt better "all over," that he no longer was conscious of aching and heaviness in the region of his heart, and that he experienced a "lightness" within his chest. He was mentally alert and appeared happy.

The following routine notes were made by the resident physician:

Twenty-one days after operation: The patient ventures that he feels much improved. He appears brighter and is able to walk about with considerably more dexterity than he showed before operation. He states that his voice is hoarse as compared with that before operation.

Twenty-five days after operation: He states that he feels better every day.

Thirty-two days after operation: He insists that he is considerably better than he was before operation. Shaving is now necessary but once in three days, whereas before thyroidectomy it was necessary daily. Examination of the vocal cords by Dr. L. M. Freedman showed paresis of one cord.

Chart 4 shows the change in the basal metabolic rate and the velocity of blood flow after operation. On the fortieth day the metabolic rate had dropped to minus 28 per cent, and the circulation time was correspondingly prolonged. The patient continued to improve, his strength returned, there was no orthopnea, and he was able to be up for short periods during the day without dyspnea. At the time of writing, two months after operation, he had no attacks of angina pectoris or cardiac asthma. He stated that he had not felt as well at any time since before the onset of his illness two years previously. There were no symptoms or signs of congestive failure. An electrocardiogram showed a slight decrease in the

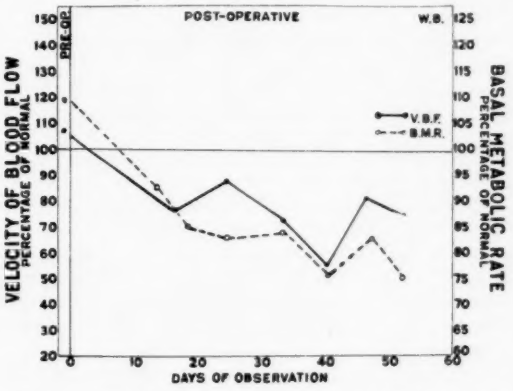

Chart 4 (case 4).—The relation between the velocity of blood flow and the basal metabolic rate.

voltage of the Q R S complexes; the pulse rate gradually dropped from a rate of from 70 to 90 per minute to a level of from 60 to 70 per minute. Before operation the hemoglobin was 82 per cent (Sahli), and the red blood count was 4,620,000. During the next six weeks the hemoglobin gradually dropped to 73 per cent (Sahli) and the red blood count to 4,080,000. The level of the systolic blood pressure was approximately 25 mm. of mercury lower after operation. There was a definite increase in the vital capacity, with an average of from 500 to 600 cc. above the preoperative level, which varied from 2,100 to 2,700 cc. During the last eight days the vital capacity had varied from 3,150 to 3,350 cc. Exercise tests caused considerably less fatigue than was present before operation with the same amount of work.

Comment.—At the time of writing, four months after operation, this patient with arteriosclerotic heart disease, angina pectoris and cardiac asthma showed significant improvement. The attacks of paroxysmal dyspnea, pain in the chest and palpitation had disappeared. He had

been up and about for short periods during the day without dyspnea. Paralleling the clinical improvement there were a persistent lowering in the metabolic rate and a slowing in the velocity of blood flow. No significant symptoms of myxedema had developed, and his mind remained alert.

CASE 5.—*Arteriosclerotic heart disease and angina pectoris for eighteen months; attacks reproducible under standard conditions.*

A. B., a man, aged 57, a German laborer, was referred to the Beth Israel Hospital through the courtesy of Dr. Joseph H. Pratt on Feb. 21, 1933. The family and past histories were irrelevant. He had always been a strong and vigorous worker until about eighteen months before admission when, while digging a ditch, he suddenly experienced a severe squeezing pain in the substernal region which forced him to cease work. This passed off after a few seconds, but recurred every time he attempted to work. He therefore left his job and rested at home for four months, but on return to work the attacks recurred. The pain did not radiate, but was frequently associated with what he described as a "tired feeling in the arms." It was relieved within a few minutes by rest and also by the administration of glyceryl trinitrate. During the past year he had been unable to work. Substernal distress occurred regularly after he had walked a few blocks and was particularly more frequent in the winter. He was seen periodically in the clinic for cardiac diseases of the Boston Dispensary during this period and in spite of treatment continued to have the same attacks.

Physical examination revealed retinal sclerosis and moderate thickening of the peripheral vessels. The left border of cardiac dulness was within normal limits; the sounds were slow, regular and of good quality. There were no murmurs. The lungs were clear. The liver was not palpable. There was no peripheral edema. The blood pressure during the first week of admission was in the vicinity of 170 systolic and 100 diastolic; thereafter it ranged from 140 systolic and 84 diastolic to 124 systolic and 70 diastolic.

Laboratory tests showed no abnormalities. These tests included examinations of the urine, phenolsulphonphthalein renal function tests, red blood cell counts, white blood cell counts, determinations of the hemoglobin, examinations of blood smears, estimations of the nonprotein nitrogen in the blood and Wassermann, Kahn and Hinton tests of the blood. The venous pressure, velocity of blood flow and basal metabolic rates were within normal limits. An electrocardiographic tracing showed normal sinus rhythm with occasional ventricular premature beats. The P R and Q R S intervals and the T waves were normal. There was no Q wave in lead III. A roentgenogram of the heart taken at a distance of 7 feet revealed no enlargement.

Exercise Tests.—This patient was a stolid phlegmatic person who minimized his symptoms, but who, nevertheless, had been unable to work for over a year and was unable to walk any great distance without attacks of substernal pain. He remained in the hospital under observation for twenty-one days, and during this time he had no anginal attacks when at rest or while exercising indoors. When he was allowed to walk outdoors in cold windy weather, however, typical anginal attacks occurred under observation. It was found that after walking from one half to three fourths of a mile he was forced to stop because of a squeezing sensation in the substernal region. After fifteen seconds of rest he was able to continue, but thereafter the attacks were precipitated more readily and after walking shorter distances. A typical experiment of this sort is shown in table 1.

The length of time and the amount of exercise necessary to precipitate the attacks of angina were found to vary from day to day. In general, the attacks were less easily produced on warm days or when there was little wind. It was found possible to precipitate anginal attacks with a greater degree of constancy when the conditions were standardized by having the patient exercise in a room the temperature of which could be kept at a constant level. For this purpose a Barach oxygen chamber filled with ordinary air was used, the temperature being kept at from 48 to 56 F. The exercise consisted of repeatedly walking up and down a flight of 2 steps, each being 9 inches high. During the experiment the patient was dressed in hospital attire consisting of cotton flannel pajamas, a cotton bathrobe, cotton socks and felt slippers. After performing from 58 to 73 trips up and

TABLE 1.—*Experiment as Performed on Patient in Case 5*

Attack	Distance from Hospital, Miles	Time Elapsing Since Start, Minutes	Time Taken for Rest, Seconds
First	0.5	7.5	15
Second	0.6	9.5	15
Third	0.7	11.5	30
Fourth	0.9	18.25	25

Temperature, 35 F.
Total distance walked, 1.15 miles.
Total time, twenty-three minutes.

TABLE 2.—*Comparison of the Production of Anginal Attacks Under Standard Conditions Before and After Operation*

Days Before Operation	Temperature of Room, F.	Patient's Weight, Pounds	Amount of Exercise, Trips	Work Performed, Ft.-Lbs.	Duration of Exercise, Minutes	Comment	Basal Metabolic Rate, Deviation from Normal, per Cent
29	56	141	65	13,750	4.4	Anginal attack	— 4
19	50	143	66	14,150	4.3	Anginal attack	— 9
18	50	143	58	12,450	3.8	Anginal attack	— 9
1	56	142	73	15,550	4.6	Anginal attack	— 5
Days After Operation							
12	50	139	142	29,600	10.0	No attack	—16
13	52	141	299	63,250	21.0	No attack	—16
23	48	144	207	44,700	15.0	No attack	—18
34	48	148	249	55,300	20.0	No attack	—18
48	53	152	383	81,600	30.0	No attack	—24

down the stairs under these conditions he was regularly forced to stop because of the development of angina pectoris. This experiment was repeated from day to day before operation and was found to give constant results.

Further Course.—The patient refused operation and returned home, but after fifteen days he returned because he found that he was unable to be up and about without precipitating substernal pain. Attacks of angina pectoris were precipitated under the same standard conditions employed before.

Total ablation of the thyroid gland was performed on April 1, 1933. Pathologic examination showed a normal gland.

The postoperative course was uneventful. The patient was allowed up nine days after operation; twelve days after the operation exercise in the cold room was repeated under precisely the same conditions as were previously employed. Angina, however, was not precipitated. Subsequently the patient was able to do more than

six times as much work as before operation without an attack of angina pectoris and without precipitating any discomfort other than slight dyspnea and moderate muscular fatigue incident to the amount of work performed (table 2). In fact, the test was terminated only because of fatigue.

Chart 5 shows the changes in the basal metabolic rates and the velocity of blood flow. The basal metabolic rate showed an immediate drop, reaching minus 18 per cent on the twenty-second day after operation. The velocity of blood flow also showed an initial slowing, but this was followed by a sharp unexplainable rise on the twelfth day after operation, followed by a drop which paralleled the drop in the basal metabolic rate.

The patient was discharged from the hospital on the fifteenth day after operation and returned for examination at frequent intervals. On May 19, the forty-eighth postoperative day, the basal metabolic rate was minus 24 per cent. The velocity of blood flow had begun to slow. Electrocardiographic tracings taken on the fifteenth and thirty-fifth days after operation showed a progressive diminution in the voltage

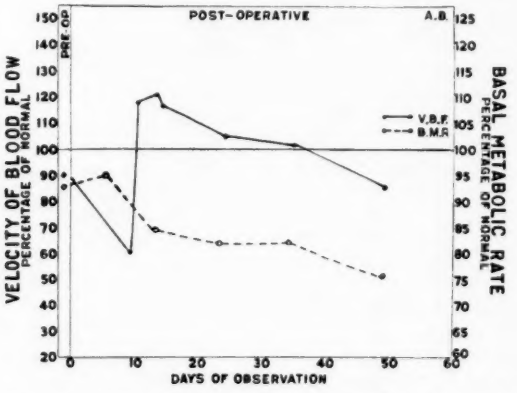

Chart 5 (case 5).—The relation between the velocity of blood flow and the basal metabolic rate.

of the Q R S complexes and an appreciable flattening of the T waves in all leads. The red blood count showed no change. The patient had been up and about, had performed light work and had not at any time experienced an attack of pain. Exercise tests, in which he was made to climb 766 steps in thirty minutes, were likewise unsuccessful in precipitating anginal attacks. His general condition was excellent, and he stated with enthusiasm that he was ready for work and looking for a job.

Comment.—This patient with a history of angina pectoris had attacks which were regularly reproducible after a given amount of exercise under standard conditions. At the time of writing, three and one-half months after operation, he had experienced no recurrence of cardiac pain. Repeated attempts to reproduce the attacks under the same standard conditions had failed, in spite of the fact that he had exercised almost to the point of exhaustion on repeated occasions.

CASE 6.—*Rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation, dyspnea and palpitation for twenty-three years; congestive failure for five years.*

B. Z., a housewife, aged 42, was first admitted to the Beth Israel Hospital on Oct. 15, 1932, complaining of palpitation, dyspnea and swelling of the legs of five years' duration. There was no history of rheumatic fever. In 1909, twenty-three years before entry, dyspnea and palpitation developed on exertion, and she coughed up blood; she was informed that she had heart trouble. In spite of slight dyspnea on exertion, she continued to work hard, married and had two children, twenty and sixteen years before admission, without the onset of congestive failure.

Approximately ten years before admission to the hospital attacks of palpitation and dyspnea, which had been very mild, became more severe and appeared after excitement and occasionally at night. Nocturnal attacks awakened her and were accompanied by dyspnea, orthopnea and vague pains in the precordial region. Pounding of the heart was distressing and persisted for from ten to fifteen minutes.

Five years before entry swelling of the ankles was noted for the first time, and three years before, edema of the legs became marked. Two years prior to admission, along with increasing cyanosis, dyspnea, palpitation and edema, the patient became orthopneic, and she noticed that the attacks of palpitation were accompanied by mild, nonradiating precordial pain which often persisted twenty-four hours or longer.

During the six months before entry the swelling of the legs, weakness, fatigue, dyspnea and palpitation became more pronounced. In spite of this, however, she continued to be up and about during the greater part of the day, but was finally forced to enter the hospital on October 15.

Physical examination showed a poorly nourished woman with moderate dyspnea and deep plum-colored cyanosis of the lips, malar prominences and tips of the fingers. With the patient sitting upright, the veins of the neck were moderately engorged. The heart was greatly enlarged, the apical impulse and left border of dulness being in the anterior axillary line. At the apex, systolic and diastolic thrills were palpable. The heart sounds were slow and absolutely irregular. At the apex the first sound was accentuated, and rough systolic and diastolic murmurs were heard. The blood pressure was 110 systolic and 70 diastolic. At the bases of both lungs there were moderate dulness and many coarse râles. The liver was greatly enlarged, reaching almost to the crest of the ileum. Deeply pitting edema of the lower extremities extended to the thighs and over the sacrum and back.

Examination of the urine and blood gave normal results except for albuminuria. The vital capacity of the lungs ranged from 1,100 to 1,700 cc. The basal metabolic rated varied from plus 4 to minus 5 per cent. The electrocardiogram showed auricular fibrillation, an inverted T^1 and marked right axis deviation. After the administration of digitalis, repeated venesection and intravenous injection of euphyllin (theophylline ethylenediamine) and salyrgan, the condition improved, diuresis occurred, and the patient lost 33 pounds (15 Kg.) of edema fluid. She was discharged fifty-one days after admission.

The patient returned home, limited her intake of fluids and salt, took a maintenance dose of digitalis and rested in bed all day, getting up only for meals and lavatory needs. The slightest departure from this regimen precipitated the symptoms and signs of congestive failure. As the patient was completely incapacitated in spite of all known medical treatment, total ablation of the thyroid gland was suggested. She was admitted to the hospital on April 3, 1933, for this procedure.

Physical examination showed slight dyspnea, orthopnea and intense plum-colored cyanosis of the lips, malar prominences and fingers. Examination of the heart gave essentially the same results as during the previous admission. At the base of the left lung there were numerous fine moist râles. The liver was non-tender, extending 4 fingerbreadths below the costal margin. There was slight pitting edema of the ankles and legs.

An electrocardiogram showed auricular fibrillation and marked right axis deviation. A roentgenogram of the heart taken at a distance of 7 feet showed great enlargement and a prominent shadow of the left auricle. The transverse diameter of the heart was 17.3 cm.; the transverse diameter of the chest, 26.4 cm. The vital capacity of the lungs varied from 1,700 to 1,880 cc. The venous pressure was 12 cm. of water. The basal metabolic rate ranged from minus 5 to minus 7 per cent. The arm to tongue circulation time varied from twenty-eight to thirty-two seconds.

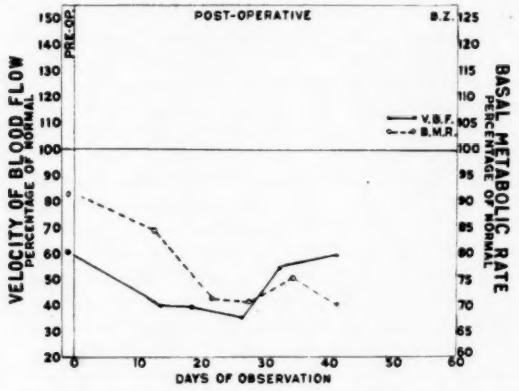

Chart 6 (case 6).—The relation between the velocity of blood flow and the basal metabolic rate.

The day preceding operation, examination of the chest revealed coarse and medium râles over both lungs posteriorly as high as the angle of the scapula.

On April 8 total ablation of the thyroid gland was performed with the patient under gas-oxygen anesthesia; the operation required one hour and thirty minutes. The thyroid gland was normal grossly and microscopically. The patient did well throughout the operation; the blood pressure varied from 90 systolic and 60 diastolic to 110 systolic and 70 diastolic, and the pulse rate, from 75 to 95 beats per minute. The postoperative course was smooth and uneventful, the temperature showing practically no rise. The respiratory rate increased from 20 to 30 per minute and continued at this level for four days, gradually returning to normal. Postoperative examination of the lungs showed râles over both lungs, but by the fourth day the right lung was entirely clear for the first time since admission. The signs on the left side had also diminished, with only a few medium-sized râles at the extreme base of the left lung. The patient was considerably calmer and remarked that she no longer felt "the pounding in her heart."

On the fourth postoperative day the patient complained of numbness and "pins and needles" sensations over the face and the distal ends of the extremities. Tests

for Chvostek's and Trousseau's signs were positive. One cubic centimeter of parathyroid extract-Collip was given immediately; 4 cc. of a 35 per cent solution of calcium chloride was given hourly, and 0.5 cc. of viosterol, 250 D, was given every six hours orally. After eight hours all symptoms had vanished. Trousseau's sign was absent, and Chvostek's sign was greatly diminished. No more parathyroid extract was given, and doses of calcium chloride were given only every three hours. The serum calcium concentration was normal throughout this time, the first analysis having been performed one hour after the institution of therapy. After seventy-two hours the serum calcium was 16 mg. per hundred cubic centimeters, and so all therapy was discontinued. On the eighth day calcium chloride therapy was again given because of a slight recurrence of symptoms. The patient felt well and was receiving calcium chloride in doses of 4 cc. three times a day.

She continued to improve, and remained unaware of her heart action. Dyspnea and cyanosis became obviously less marked. Chart 6 shows the changes in the basal metabolic rate and the velocity of blood flow. On the nineteenth day after operation the metabolism fell to minus 37 per cent, and the circulation time, which was prolonged to start with, became somewhat slower. Electrocardiograms showed no change. The vital capacity became slightly increased, the highest reading before operation being 1,800 cc. as compared with 2,150 cc. afterward. With the lowering of the metabolic rate, mild secondary anemia developed, the red count decreasing from 5,780,000 per cubic millimeter to 4,060,000; the hemoglobin dropped from 92 to 75 per cent on the twenty-seventh day after operation.

The patient's general improvement was striking. She was able to sleep soundly without orthopnea, and on the twentieth day after operation she was permitted to be up and about the wards. She took short walks without any evidence of shortness of breath and maintained that she had not felt so well for at least ten years. The liver was no longer palpable, and except for an occasional râle at the base of the left lung there were no signs of congestive failure.

An interesting result of operation has been her increased calmness. Although a cooperative patient, she was very sensitive and easily excited, her apical rate often rising 60 beats above the basal level at the mere approach of the visiting physician. Since operation, this excitability has conspicuously lessened.

Comment.—At the time of writing, three and one-half months after operation, this patient with rheumatic heart disease and signs of circulatory failure of twenty-three years' duration showed conspicuous improvement. Palpitation and dyspnea on slight exertion had disappeared. She was able to lie flat in bed without distress. Cyanosis, which was striking before operation, had become appreciably less, and she had shown steady improvement even after being up and about for two and one-half months. The basal metabolic rate had decreased, and the velocity of blood flow had correspondingly slowed.

CASE 7.—*Hypertensive heart disease, attacks of cardiac asthma for two years; conspicuous improvement after operation; sudden attack of pulmonary edema, and death twenty-one days after operation.*

W. L., an ex-bartender, 60 years of age, was admitted to the Beth Israel Hospital on March 23, 1933, complaining of shortness of breath of two years' duration. The past history was unimportant. The present illness began two years before entry with sudden attacks of coughing and difficulty in breathing which lasted from fifteen to twenty minutes. At the same time he noticed short-

ness of breath on exertion, and while driving his car he often experienced sudden spells of breathlessness. One year before admission the symptoms became more pronounced and more frequent. The attacks were not attended with pain and rarely occurred at night. Six weeks before admission he was forced to go to bed because of attacks repeated two or three times a day. Despite several weeks of rest the symptoms continued. Five days before admission he was seized with an unusually severe attack which lasted for about an hour and was accompanied by wheezing and marked prostration. At this time moderate swelling of the legs and some swelling of the right hand developed. Because the paroxysmal attacks of dyspnea continued in spite of all medical treatment he was referred to the hospital.

Physical examination revealed a swarthy, somewhat pale, lethargic man propped up in bed in respiratory distress with cyanosis of the lips and cheeks. The retinal vessels were narrowed and sclerosed. Percussion revealed enlargement of the heart, the left border being 10 cm. to the left of the midsternal line. The sounds were slow and regular. There were a systolic murmur at the apex and a rough systolic murmur at the aortic area. The blood pressure was 220 systolic and 90 diastolic. At the bases of both lungs and in the left anterior axillary region fine and medium moist râles were heard. The liver was enlarged to 4 fingerbreadths below the costal margin. There were clubbing and cyanosis of the tips of the fingers. There was no clinical evidence of thyrotoxicosis.

The urine contained a slight trace of albumin, and the specific gravity varied from 1.010 to 1.022. The greatest excretion of phenolsulphonphthalein in two hours and ten minutes was 25 per cent in five successive tests. The red blood count was 3,950,000 per cubic millimeter; the hemoglobin was 65 per cent, and the white blood cells numbered 18,400, with a normal differential count. A roentgenogram of the heart taken at a distance of 7 feet showed transverse enlargement of the heart with prominence of the left ventricle. The transverse diameter of the heart was 16.1 cm.; the transverse diameter of the chest was 28.7 cm. An electrocardiogram showed normal sinus rhythm, the rate being 70, inverted T waves in all three leads and a P R interval of 0.25 second. The vital capacity of the lungs on admission was 1,200 cc.; this gradually rose to 2,300 cc. before operation. The venous pressure varied from 7 to 8 cm. of water. The velocity of blood flow was slowed; the arm to tongue circulation time varied from thirty to thirty-one seconds. The basal metabolic rate was plus 21 per cent, plus 24 and plus 21 per cent on three different days.

During the first twenty-four hours after admission the patient had several brisk attacks of paroxysmal dyspnea requiring morphine for relief, but during the next three days the attacks became less frequent and less severe. Gallop rhythm was noted on many examinations, and moist râles persisted at the bases of both lungs.

On April 11 total ablation of the thyroid gland was performed with the patient under gas-oxygen anesthesia, the operation requiring two hours. The patient's general condition was excellent throughout. The blood pressure did not rise above 220 systolic and 90 diastolic. The pulse rate varied from 100 to 130. The temperature rose to 103.5 F. on the first day after operation, returning to normal the next day. The pulse returned to normal on the fourth day after an initial rise to 120.

Pathologic examination of the thyroid gland showed a quiescent colloid nodular goiter. There was cystic degeneration of a removed parathyroid glandule.

The patient made a good recovery and was quite cheerful and talkative a few hours after the operation. He continued to be in excellent spirits, minimizing any

discomfort and maintaining that he felt better. His voice was husky for a few days, but both cords moved well. Examination of the lungs revealed a moderate number of medium and crackling râles at the bases of both lungs, extending as high as 3 fingerbreadths below the angle of the scapula.

Three days after operation the râles at the bases of both lungs had considerably diminished. Seven days after operation the patient insisted that his mind was considerably clearer than before operation. He said that before operation he was "dead" and hardly knew that he was in a hospital. He took a lively interest in everything and appeared much improved. On the twelfth day after operation he was permitted to get out of bed and gradually increase his activity. He then noticed that there was considerably less palpation on exertion than he had experienced before operation. Walking up and down the corridor briskly caused no perceptible dyspnea. He regained strength and gained 6 pounds (2.7 Kg.). The vital capacity was in the vicinity of 2,150 cc. each day. The metabolic rate dropped from a level of plus 21 per cent to minus 4 per cent on the fifteenth day after operation. The velocity of blood flow showed a slight slowing at this time.

The patient continued to improve. His mind became clearer, orthopnea disappeared entirely, and the cyanosis diminished. He was up and about the wards without dyspnea or discomfort. The râles disappeared from the bases of both lungs, the liver could no longer be felt, and he stated that he had not felt so well for five years. His wife corroborated this statement and was enthusiastic over his improvement. The blood pressure continued to be elevated at 220 systolic and 110 diastolic.

On the twenty-first day after operation at about 10:00 p. m., the patient suddenly experienced paroxysmal dyspnea; he became acutely orthopneic and began to cough up large amounts of bloody froth. There was no pain. The blood pressure rose to over 300 systolic (the manometer used recorded only to 300 mm.). His condition of intense dyspnea with the coughing up of large amounts of frothy bloody sputum continued. Morphine, tourniquets applied to the extremities, venesection, intravenous injections of dextrose, an oxygen tent and, finally, intracardiac injections of epinephrine and a Drinker respirator were employed without effect. The patient died two hours after the onset of the attack.

Autopsy showed a large heart weighing 660 Gm., with marked hypertrophy of the left ventricle. The lungs showed chronic passive congestion throughout with additional pulmonary edema in the upper lobes. There was bilateral hydrothorax of 500 cc. in each cavity.

Comment.—This patient with hypertensive heart disease and attacks of cardiac asthma increasing in severity during the two years before operation showed striking improvement after thyroidectomy. His palpitation and respiratory distress disappeared; râles that had been present at the bases of both lungs entirely cleared; cyanosis diminished, and his mind became clearer than it had been before operation. He regained strength, was able to walk briskly up and down the corridor without dyspnea and stated that he had not felt so well for five years. On the twenty-first day after operation, however, after being out of bed the entire day for ten days, he suddenly experienced an attack of pulmonary edema and in spite of all efforts died two hours later.

CASE 8.—*Rheumatic heart disease, mitral stenosis and insufficiency and dyspnea for fourteen years; hemoptysis and congestive failure for one year.*

W. D., an American, aged 23, a bus boy, was admitted to the Beth Israel Hospital on April 11, 1933, complaining of shortness of breath on exertion, fourteen years in duration. There was no history of rheumatic fever. The present illness began at the age of 9 when he was referred to the Lawrence General Hospital. Physical examination at that time showed the characteristic thrill and murmurs of advanced mitral stenosis and insufficiency. He remained in bed for six weeks, but on attempting to resume normal life found that the usual activities of childhood caused him to become very short of breath. At the time he was conscious of a choking sensation and pain in the region of the heart which often radiated to the left shoulder. During the next thirteen years there was only a slight increase in symptoms. Thirteen months previously, however, he suddenly began to cough up large amounts of blood, averaging three cupfuls daily for several days. During this attack he was sent to the Boston City Hospital, where he remained in bed for six weeks. He returned home and was fairly comfortable, spending the greater part of the day in bed. The slightest departure from this regimen, however, caused severe dyspnea. For this reason he was transferred to a hospital for chronic diseases where, except for occasional attacks of hemoptysis, he was fairly comfortable for three months, following which he again had intense dyspnea, orthopnea and palpitation which persisted for three and a half months. When seen in February, 1933, he was considered too sick for any operative procedure. On continued rest in bed his condition improved somewhat, and he was transferred to the Beth Israel Hospital for study and operation.

Physical examination showed good development, mental alertness, slight dyspnea, orthopnea and cyanosis of the cheeks, nose and lips. The left anterior part of the chest showed a marked bulging deformity. A diastolic thrill was palpable at the apex, and the impulse was seen and felt in the fifth space 10 cm. from the midsternal line. The sounds were slow and regular; the first sound, at the apex, was loud and booming; the second pulmonic sound was accentuated. There were a loud rumbling crescendo diastolic murmur and a loud blowing systolic murmur in the mitral area. The lungs were clear throughout. The blood pressure was 110 systolic and 72 diastolic.

Examinations of the urine and blood gave normal findings. A roentgenogram taken at a distance of 7 feet showed moderate cardiac enlargement, the transverse diameter being 17.8 cm.; the internal diameter of the chest was 30 cm. An electrocardiogram showed sinus rhythm with auricular premature beats, large and notched P waves in leads I and II, a P R interval of 0.22 second and right axis deviation. The venous pressure was approximately 5 cm. of water; the arm to tongue circulation time by the decholin method varied from fifty to fifty-two seconds; the basal metabolic rate was minus 8 per cent.

On the day preceding operation, with the patient semirecumbent, there were cyanosis of the face and engorgement of the veins of the neck, and a distinct protodiastolic gallop rhythm was noted at the apex. There was Cheyne-Stokes respiration. The liver was palpable on deep inspiration, and the edge was definitely tender. There was slight pitting edema of the legs.

Total ablation of the thyroid gland was performed on April 15 with the patient under gas-oxygen anesthesia; the operation required two hours and twenty-two minutes. Just before operation the patient appeared excited. The heart rate was 94, and on palpation of the radial pulse there was definite pulsus alternans; this observation was corroborated by measurements of the blood pressure. During the course of operation the pulsus alternans disappeared. The blood pressure varied from 110 systolic and 80 diastolic to 105 systolic and 80 diastolic; the pulse rate ranged from 120 to 100. Fifteen minutes after operation the patient talked. His lungs were clear, and his general condition was excellent.

The next day a few medium and fine crackling râles were heard at the bases of both lungs. Except for two transient rises to 100 F., there was practically no elevation in the pulse or the temperature following the operation.

The following notes were made by the resident physician:

April 19 (four days after operation): The patient is feeling comfortable. It is too early to judge the effects of operation.

April 26 (eleven days after operation): The patient volunteers that he no longer has the pounding in his chest that was always present before operation. He is considerably more alert and more given to smiling than at any previous time.

On the second postoperative day there was a slight Chvostek sign on the left side of the face which continued to be present occasionally during the next ten days. The patient was given 8 cc. of a 35 per cent solution of calcium chloride four times a day and once at night, and 0.5 cc. of viosterol twice a day. Chart 7 shows the changes in the basal metabolic rate and the velocity of blood flow. The

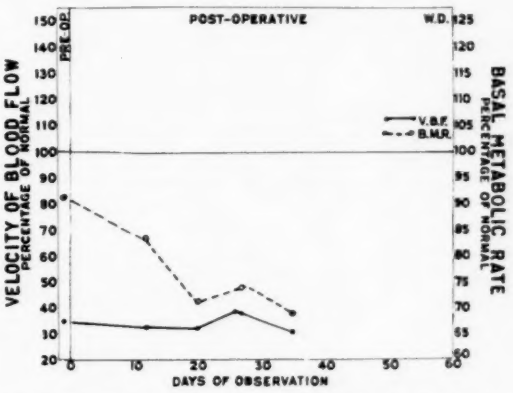

Chart 7 (case 8).—The relation between the velocity of blood flow and the basal metabolic rate.

basal metabolic rate fell rapidly, reaching minus 30 per cent on the twentieth day after operation. The arm to tongue circulation time, which had been prolonged to fifty-two seconds on admission, became fifty-seven seconds on the twentieth postoperative day.

Successive electrocardiograms showed a definite flattening of the T waves, particularly in lead I. The voltage of the Q R S complexes showed no appreciable change. There was a successive increase in the P R interval from 0.20 second before operation to 0.25 second one month after operation. The vital capacity showed a definite rise of approximately 400 cc. above the preoperative level, the highest reading before operation being 2,400, and that after operation, 2,800 cc. The red blood count showed no change, being 5,430,000 six weeks after operation.

The patient slept soundly. Although he still preferred one or two pillows at night, he could lie perfectly flat without discomfort. Breathing was notably easier. On the twelfth day after operation he was permitted out of bed. At the time of writing he had been up and walking without dyspnea or fatigue for one month. There had been no hemoptysis.

Repeated exercise tolerance tests showed marked improvement. There were considerably less dyspnea and fatigue, and the pulse returned to its resting level within one-half the time recorded in the preoperative performances. Whereas the preoperative tests caused the blood pressure to fall after exercise, the tests made after operation showed the normal sharp rise.

The patient stated that he was more comfortable and felt better than he had at any time during the preceding three years.

Comment.—At the time of writing, three months after operation, this patient with rheumatic heart disease, dyspnea of fourteen years' duration and attacks of congestive failure of one year's duration showed conspicuous improvement. Palpitation, orthopnea and dyspnea had disappeared. During the past month he had walked from 2 to 3 miles a day without fatigue, dyspnea or any evidence of congestive failure. Paralleling this improvement, the basal metabolic rate dropped to minus 30 per cent and remained low.

CASE 9.—*Rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation and attacks of congestive failure for twenty-six years.*

L. B., a Canadian housewife, aged 45, was referred to the Beth Israel Hospital on April 12, 1933, through the courtesy of Dr. Otto C. Yens. Shortness of breath had been present for thirty-two years. She had diphtheria at the age of 7 and never quite recovered her full strength. At the age of 12 she had rheumatic fever with symptoms in the joints persisting for three months; since then shortness of breath and palpitation on slight exertion had always been present. She was able to go to school, however, and later did light work, but always was conscious of her physical limitations. At the age of 19, twenty-six years before admission, she had a severe attack of epistaxis, and one year later she was forced to bed with marked palpitation, dyspnea and moderate edema of the extremities. Several weeks were spent at a convalescent home, but when she returned home dyspnea and palpitation reappeared. Each year, from 1909 to 1927, she had dyspnea and edema of the legs. Following pneumonia in 1927 orthopnea became significant, and from that time on dyspnea and palpitation on exertion was so pronounced that the patient was unable to spend more than two or three hours a day out of bed. During the past ten years she had a more or less continuous pressure and a dragging sensation in the left anterior part of the chest and sharp pain on exertion. Edema had been less marked during the last five years, although it was present most of the time.

Physical examination in the hospital, after the patient had been completely at rest in bed at home for a month, revealed a pale, well developed, middle-aged woman propped up in bed with slight dyspnea and with moderate cyanosis of the lips, nose and cheeks. The veins of the neck and arms were moderately engorged with the patient in the upright position. The apex impulse was felt at the sixth interspace in the anterior axillary line. The heart sounds were slow and absolutely irregular; the first sound at the apex and the second pulmonic sound were accentuated. The ventricular rate was 68. A rumbling diastolic murmur and a harsh blowing systolic murmur were heard in the mitral area. The lungs were clear. The blood pressure was 140 systolic and 80 diastolic. The edge of the liver was nontender and barely palpable. There was slight pitting edema of the tibiae.

Examination of the urine gave normal results. There was slight secondary anemia, the red blood count being 4,290,000 and the hemoglobin 77 per cent. A

roentgenogram of the chest taken at a distance of 7 feet showed the transverse diameter of the heart to be 13.9 cm. and the internal diameter of the chest 22 cm. The right auricle was prominent. An electrocardiogram showed auricular fibrillation with a slow ventricular rate, erect T waves in leads I and II and right axis deviation. The vital capacity of the lungs varied from 1,750 to 1,850 cc., the venous pressure, from 10 to 12 cm. of water. The arm to tongue circulation time ranged from seventeen to nineteen seconds; the basal metabolic rate was minus 10 per cent.

On April 17, total ablation of the thyroid gland was performed with the patient under gas-oxygen anesthesia; the operation required one hour and thirty minutes. The patient's condition remained excellent throughout. The blood pressure did not rise above 120 systolic, nor the pulse above 90 per minute. There was practically no postoperative reaction, the temperature being 100 F. on the second day, with a return to normal on the third day after operation.

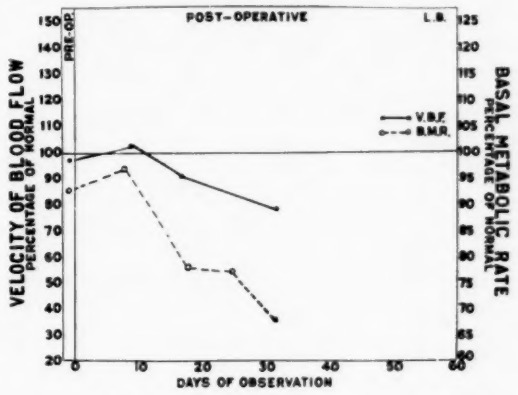

Chart 8 (case 9).—The relation between the velocity of blood flow and the basal metabolic rate.

On the seventh postoperative day the patient stated that she felt considerably easier and volunteered that there was much less palpitation with a change in position. This symptom had been constant for years before operation. She noticed that she was able to breathe easier and that she could sleep on the left side, something she had been unable to do for six years; she used fewer pillows at night. The following routine notes were made by the resident physician:

May 5 (eighteen days after operation): During the past ten days there has been a definite change in the patient's appearance and general attitude. She is more calm, looks more rested and complains less frequently. She states and demonstrates that she is able to move about quite freely without the return of palpitation.

May 12: The patient has increased her activities and has been up and about in a wheel chair without noticing fatigue. Breathing has continued to improve without evidence of dyspnea in the course of getting in and out of bed. Orthopnea is definitely less marked than it was one week ago, although she still sleeps in a semirecumbent position. Other than a slight dull pain in the region of the precordium which was present on awaking this morning and which persisted for ten

minutes, there has been no return of the preoperative pain which had been constant for years.

Chart 8 shows the changes in the basal metabolic rate and the velocity of blood flow. On the eighteenth day after operation the metabolism had fallen to minus 22 per cent, and the arm to tongue circulation time was prolonged. Electrocardiographic tracings made fifteen days after operation showed appreciable flattening of the T waves and a decrease in the voltage of the Q R S complexes. The vital capacity showed a slight but persistent increase, the highest reading before operation being 1,850 cc., and that after operation, 2,050 cc. The red blood cell count and hemoglobin showed no appreciable change. An exercise test performed before operation resulted in marked dyspnea, prostration and almost collapse when less than half the standard amount of work was performed. Thirty-two days after operation the same amount of exercise was accomplished without discomfort and with very slight dyspnea; the blood pressure returned to the resting level within two minutes, compared with nine and a half minutes before operation. The patient continued to improve and was able to be up and about without dyspnea or fatigue. The pressure pain in the region of the heart that was continuous for more than ten years before operation disappeared. The patient stated that she had not felt so well at any time during the preceding six years.

Comment.—Three months after operation, this patient with rheumatic heart disease and attacks of congestive failure of twenty-six years' duration showed striking improvement. Palpitation, dyspnea and orthopnea had disappeared. She was able to be up and about without signs of congestive failure. Before operation a standardized amount of exercise almost precipitated collapse, but at the time of writing the patient was able to perform the same exercise with little or no dyspnea and with a more normal response of the pulse and blood pressure. Corresponding to the clinical improvement the basal metabolic rate became lowered and the velocity of blood flow prolonged.

CASE 10.—*Bronchial asthma for twenty-nine years; erythrocytosis, cor pulmonale and right ventricular heart failure with edema for five years.*

F. C., a man, 31 years of age, was transferred from the Massachusetts General Hospital through the courtesy of Dr. James H. Means on April 13, 1933. He gave a history of bronchial asthma twenty-nine years in duration. At the age of 2 a generalized eczematous rash and attacks of wheezing developed. These attacks occurred weekly up until the age of 9, when they became more severe, necessitating the upright position during sleep. Between the age of 10 and 20 years attacks occurred approximately two or three times a week and generally awoke him out of a sound sleep. This continued until five years prior to admission, when the attacks became less frequent and severe. About that time, however, he noticed that he was always short of breath on exertion. In 1929 dyspnea suddenly increased, and widespread edema developed on the legs, trunk and face. There was moderate palpitation of the heart but no pain in the chest. The patient was sent to the Massachusetts General Hospital, where he remained for several months; under the influence of diuretics he lost 54 pounds (24.5 Kg.). He returned to work with restricted activity, but after a few months again had dyspnea on exertion and edema of the legs. He was admitted to the Massachusetts General Hospital four times, the interval between successive admissions becom-

ing progressively shorter. After the third admission he returned home and, except for one hour daily, was confined to bed. In spite of this rest, shortness of breath and moderate edema of the legs recurred, necessitating his return to the hospital after only seventeen days at home. Asthmatic attacks had occurred daily. During this admission it was the opinion of Dr. Means that the patient's reserve was so limited that he would be a cardiac invalid the remainder of his life. He therefore placed the possibility of total ablation of the thyroid gland before the patient for decision, clearly stating its experimental nature.

Physical examination on admission to the Beth Israel Hospital after six weeks of rest in bed at the Massachusetts General Hospital revealed a dark-skinned, conspicuously cyanotic young man with moderate respiratory distress. The chest was definitely emphysematous; there was narrowing of the costal angle on inspiration. The cardiac apex was barely felt in the fifth intercostal space just within the nipple line. The left border of dulness was 9.5 cm. from the midsternal line.

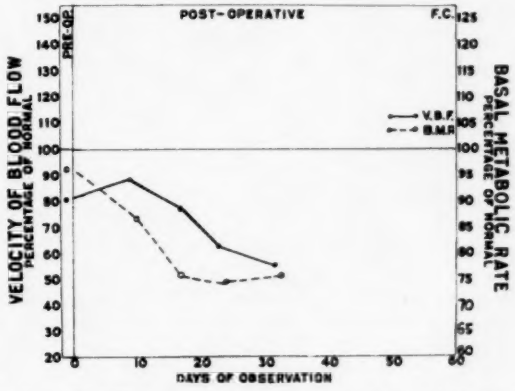

Chart 9 (case 10).—The relation between the velocity of blood flow and the basal metabolic rate.

The sounds were slow, regular and of good quality. There were no murmurs. The blood pressure was 120 systolic and 70 diastolic. The lungs were hyperresonant to percussion, and at the bases numerous crackles and sibilant rhonchi were heard. The edge of the liver was not felt. There was no edema of the extremities.

Examination of the urine gave normal results. The red blood cell count was 6,420,000 per cubic millimeter; the hemoglobin was 89 per cent; the white blood count was 8,500, and the smear was normal. A roentgenogram of the heart taken at a distance of 7 feet showed slight enlargement, especially to the right, the transverse cardiac diameter being 15.1 cm.; the internal diameter of the chest was 27.1 cm. An electrocardiogram showed a normal sinus rhythm, a ventricular rate of 80, inverted T waves in leads II and III, a P R interval of 0.20 second and right axis deviation. The vital capacity of the lungs varied from 1,900 to 2,400 cc.; the venous pressure, from 4 to 6 cm. of water, and the arm to tongue circulation time, from twenty to twenty-three seconds. The basal metabolic rate was found to vary between minus 5 and minus 2 per cent.

On April 18, 1933, total ablation of the thyroid gland was performed. The patient's condition was excellent throughout the operation. The blood pressure

varied from 120 systolic and 100 diastolic to 130 systolic and 90 diastolic. The pulse rate remained below 105. After operation the temperature rose to 101 F., the pulse rate to 120 and respiratory rate to 35. After the third postoperative day the temperature, pulse and respirations were normal.

Slight hoarseness was present after the operation, but the vocal cords appeared normal. On the fourth day the patient stated that the pounding of his heart which had been present before operation had become appreciably less. The cardiac rate gradually slowed from 88 to 70 per minute. The cough diminished, but the pulmonary signs showed no change. On the eighth postoperative day the patient stated: "My breathing is much better now than it was before the operation. I used to have an asthmatic attack every damp day and that would continue until the damp weather ended. I have not had an attack since the operation." He noted that before operation he could not lie flat without a choking sensation, whereas after operation he preferred to sleep almost completely recumbent without discomfort. During the two weeks previous to the operation he had five asthmatic attacks. In spite of damp weather during twenty-nine days after operation, there was not the slightest wheezing. On May 17 and 18, one month after operation and during the season when the paroxysms had been most severe, he had two mild spells of wheezing which persisted for a few minutes and caused him little or no discomfort. He sleeps soundly without orthopnea. The vital capacity of the lungs increased from 2,400 to 3,100 cc. on the fourteenth day after operation. This level was sustained for five days, after which there was a decrease, the vital capacity still remaining about 300 cc. above the preoperative level. Chart 9 shows the changes in the basal metabolic rate and the velocity of blood flow. The basal metabolic rate showed a fall to minus 24 per cent on the sixteenth day. The velocity also slowed. The red blood count and hemoglobin were unchanged. An electrocardiogram showed a decrease in the height of the T wave in all leads.

The patient was permitted out of bed on the seventh day after operation. At the time of writing, somewhat over a month after operation, he had been on his feet the entire day for three weeks without any evidence of circulatory insufficiency. Exercise tolerance tests showed a striking improvement since operation. On May 19, one month after operation, he was able to perform twice the amount of work performed before without dyspnea or fatigue. He was able to perform the standard exercise tolerance test with a normal return of the blood pressure and pulse to the previous basal level within two minutes.

Dr. James H. Means, under whose care the patient had been at the Massachusetts General Hospital and who saw the patient on May 1, 1933, the thirteenth postoperative day, made the following note: "In my opinion, this is a remarkable result. I have known the patient for several years and his appearance is now unlike anything I have seen in him before. He is far less cyanotic and is really without dyspnea or orthopnea. His pulse is only 78 after walking around the ward. Of course, if his asthma becomes bad again he may get into trouble. Nevertheless, there is no doubt in my mind that his outlook in general has become vastly improved by the thyroidectomy."

The patient maintained that he felt better than at any time during the preceding seven years.

Comment.—This patient with cor pulmonale and congestive failure of five years' duration occurring as a result of long-standing bronchial asthma and chronic pulmonary emphysema showed significant improvement after thyroidectomy. Palpitation and dyspnea disappeared, and

he slept soundly in the recumbent position. He was able to perform more work without dyspnea or fatigue than was possible before operation. His attacks of bronchial asthma have become strikingly less frequent and less severe. Clinical improvement paralleled the fall in the basal metabolic rate and the changes in the velocity of blood flow.

CASE 11.—*Résumé of findings in case 3 (G. F.) of a previous communication*[1] *with report of the subsequent clinical course. Rheumatic heart disease, mitral stenosis, auricular fibrillation, angina pectoris and congestive failure for three years prior to operation. Clinical course six months following operation.*

G. F., a man, aged 52, an unemployed chef, entered the hospital complaining of shortness of breath, palpitation, substernal pressure and weakness of three years' duration. At the age of 12 he had rheumatic fever which forced him to remain in bed for three months. After this, however, he felt quite well until three years prior to examination, when while working he suffered an attack of severe precordial pain which radiated down both arms to the tips of the fingers. He became extremely dyspneic and was forced to remain in bed for three days. He returned to work, but two and a half months later was again forced to stop and enter a sanatorium because of increasing dyspnea. After a few months of rest he felt well except for a sense of substernal pressure, but on attempting to work he became short of breath and was again forced to go to bed. Dyspnea and attacks of substernal pain gradually became more and more severe in spite of the fact that he refrained from work and rested the greater part of the day. The attacks of substernal pain appeared frequently and were not necessarily brought on by effort; they appeared while the patient was at rest and sometimes during sleep. They lasted for several minutes and were regularly relieved by the administration of glyceryl trinitrate; during a period of prolonged rest in bed they were absent. For two years before admission he had gradually increasing edema of the legs, and during the last few months this was present every time he spent a few hours on his feet, in spite of prolonged rest in bed.

Physical examination on admission, after complete rest in bed for many months, showed orthopnea, slight cyanosis of the lips and mucous membranes, marked enlargement of the heart, grossly irregular heart sounds and a faint middiastolic murmur below and to the left of the nipple; there was no aortic diastolic murmur. The liver was enlarged and tender, there was definite pitting edema of the legs and sacrum, and scattered moist râles were heard over the bases of the lungs. The diagnosis was auricular fibrillation, congestive heart failure, mitral stenosis, regurgitation and, probably, old healed coronary thrombosis.

Total ablation of the normal thyroid gland was performed on Dec. 15, 1932, and the patient had an uneventful convalescence. The basal metabolic rate fell gradually, reaching minus 14 per cent two weeks after operation and minus 28 per cent four weeks after operation. The change in the clinical condition was conspicuous. The patient was no longer orthopneic; his craving for water entirely disappeared, and he failed to show any evidence of edema. He was able to undertake moderate exercise without dyspnea or signs of congestive failure, whereas before operation even combing his hair or turning over in bed caused violent palpitation. He stated that for the first time in three years he was unaware that he had a heart. The sense of thoracic compression with numbness and occasional pain in the left arm did not reappear, and in spite of the lowered metabolism and somewhat increased sensitivity to cold his mental processes became more acute than they were prior to operation.

TABLE 3.—*Summary of the Effects of Total Abl*

Case, Sex and Age	Diagnosis	Duration of Cardiac Decompensation	Before and Days After Operation	Basal Metabolic Rate, Percentage Deviation From Normal	Arm to Tongue Circulation Time, Seconds	Dyspnea	Orthopnea†	Palpitation	Card Pa
1 M 27	Rheumatic heart disease; mitral stenosis and insufficiency	5 years	Before	+ 5	23	Moderate at rest	Intense	Intense at rest	Almo const
			48 days	—22	45	Slight on exertion	Absent	Absent on exertion	Abse
2 M 22	Rheumatic heart disease; mitral stenosis; aortic insufficiency; auricular fibrillation; extreme cardiac enlargement; pulmonary and renal infarction	12 years	Before	— 3	42	Slight at rest	Intense	Intense at rest	Const
			52 days	—30	66	Slight on exertion	Absent	Absent on exertion	Absent with pu nary e
3 M 66	Arteriosclerotic heart disease	6 years	Before	+ 9	32	Intense on exertion	Slight	Constant at rest	Slig
			17 days	—23	68	Slight on exertion	Absent	Absent on exertion	Abse
4 M 55	Arteriosclerotic heart disease; hypertension; angina pectoris; cardiac asthma; Paget's disease	2 years	Before	+11	17	Intense on exertion	Slight	Absent	Abse
			43 days	—24	24	Slight on exertion	Absent	Absent	Abse
5 M 57	Arteriosclerotic heart disease; angina pectoris	18 months	Before	— 9	22	Absent	Absent	Absent	Abse
			48 days	—24	21	Absent	Absent	Absent	Abse
6 F 42	Rheumatic heart disease; mitral stenosis and insufficiency; auricular fibrillation	5 years	Before	— 6	30	Moderate at rest	Moderate	Intense at at rest	Mode
			41 days	—30	31	Slight on exertion	Absent	Slight on exertion	Abse
7 M 60	Hypertensive heart disease; cardiac asthma	2 years	Before	+21	30	Moderate at rest	Moderate	Moderate on exertion	Abse
			15 days	— 4	30	Slight on exertion	Absent	Absent	Abse
8 M 23	Rheumatic heart disease; mitral stenosis and insufficiency	18 months	Before	— 8	52	Slight at rest	Intense	Intense	Slig
			34 days	—32	58	Moderate on exertion	Slight	Absent	Abse
9 F 45	Rheumatic heart disease; mitral stenosis and insufficiency; auricular fibrillation	26 years	Before	—10	19	Slight at rest	Intense	Intense	Inte
			32 days	—32	23	Moderate on exertion	Slight	Slight	Slig
10 M 31	Cor pulmonale; asthma 29 years	5 years	Before	— 5	23	Moderate at rest	Intense	Moderate	Abse
			31 days	—24	32	Slight on exertion	Absent	Absent	Abse

* On the twenty-first day after operation, pulmonary edema developed in the patient, and he died two hours after the
† Observations of orthopnea were made at the time of admission, whereas measurements of venous pressure were

	Hemoptysis	Miscellaneous Symptoms	Peripheral Edema	Râles	Hepatic Enlargement	Cyanosis	Heart Rate, Beats per Minute	Respiratory Rate, per Minute	Blood Pressure, Mm. Hg	Vital Capacity, Cc.	Venous Pressure, Cm. of Water
...gh	Almost daily	.....	Slight at rest	Present at base of left lung	Slight	Slight	72-100	20-36	100/60	3,500 to 3,600	8
...nt	Absent	.....	Absent on activity	Absent	Absent	Absent	80-90	20	100/64 to 120/74	3,000 to 3,250	11
...ler- ...e	Frequent	Occasional attacks of pulmonary infarction	Absent at rest	Present at bases of both lungs	Absent	Absent	70-90	20-30	104/70 to 120/70	2,800 to 3,100	11
...nt	Absent	Three attacks of pulmonary infarction	Absent on activity	Absent	Absent	Absent	50-60	20	120/70	2,900 to 3,350	11
...se	Absent	.....	Absent at rest	Absent	Absent	Absent	50-60	20-24	130/60 to 110/70	2,700 to 3,300	3
...ht	Absent	.....	Absent on activity	Absent	Absent	Absent	50-60	20	120/70	3,700 to 3,950	2
...nt	Absent	.....	Absent at rest	Absent	Absent	Absent	70-90	20-24	180/110 to 150/70	2,100 to 2,700	4
...nt	Absent	.....	Absent on activity	Absent	Absent	Absent	60-70	20	140/90	3,150 to 3,350	3
...nt	Absent	Angina pectoris on exertion	Absent	Absent	Absent	Absent	70-80	20	140/70	3,900	3
...nt	Absent	No angina pectoris	Absent	Absent	Absent	Absent	64-70	20	158/112	3,750	4
...nt	Absent	.....	Slight at rest	Intense at bases of both lungs	Intense	Intense	44-62	20	118/62 to 130/72	1,700 to 1,800	12
...nt	Absent	.....	Absent on activity	Slight at base of left lung	Absent	Slight	38-44	20	122/80	1,800 to 1,900	9
...nt	Absent	Frequent cardiac asthma attacks	Slight at rest	Moderate at bases of both lungs	Intense	Moderate	68-80	20	190/110	1,600 to 2,300	7
...nt	Absent	No asthmatic* attacks for 20 days	Absent on activity	Absent	Absent	Absent	68-72	20	210/118	1,700 to 2,150	8
...nt	Occasional	....	Absent	Absent	Absent	Slight	60-80	20-24	110/72	2,000 to 2,400	5
...nt	Absent	.....	Absent	Absent	Absent	Absent	60-70	18-20	120/80	2,300 to 2,700	6
...nt	Absent	.....	Slight at rest	Absent	Slight	Moderate	60-80	20-24	134/80	1,750 to 1,880	12
...nt	Absent	.....	Absent on activity	Absent	Absent	Slight	45-50	20-24	118/84	1,900 to 2,050	10
...se	Absent	Frequent severe asthmatic attacks	Absent	Moderate râles and rhonchi	Absent	Intense	84-100	20	104/80 to 120/80	1,900 to 2,400	6
...d to ...nt	Absent	Two slight attacks of wheezing	Absent	Râles absent; rhonchi present	Absent	Slight	68-80	20	118/84	2,750 to 3,100	2

...after the ... attack.
...sure were ... days later.

Approximately three and a half months after operation the patient was given work in the hospital in order to keep him under observation and to follow the course of his convalescence. His position demanded the transportation of bottles and medicines from one part of the hospital to another and kept him on his feet for approximately eight hours a day. He worked six and one-half full days a week and continued at this work for two weeks without complaint and without showing any evidence of circulatory insufficiency. There was no dyspnea, orthopnea, cyanosis or edema, and the lungs remained clear. He was later engaged as a helper in the research laboratory. At the time of writing he had been occupied in this capacity, working eight hours daily, for two months.

Six months after operation, with normal activity and work, he continued to maintain good health and showed no evidence of congestive failure. He had no complaints except for a few symptoms referable to the gastro-intestinal tract. There had been no attacks of angina pectoris, and palpitation appeared only follow-

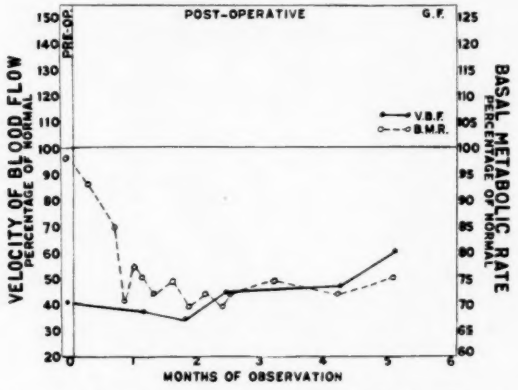

Chart 10 (case 11, or case 3 of previous communication).—The relation between the velocity of blood flow and the basal metabolic rate.

ing excessive effort. On May 16, 1933, five months after operation, he performed an exercise test without any evidence of dyspnea. He was able to walk a mile or more without dyspnea, and he could continue were it not for the sense of fatigue in his legs. He stated that he actually felt better after a given amount of exercise and for this reason took long walks regularly. The vital capacity increased after operation and continued at a level of approximately 500 cc. higher than it was prior to operation; the last readings varied from 2,900 to 3,200 cc.

The patient had a somewhat yellowish pallor, and the skin, particularly of the soles and palms, had become dry. The growth of hair had been noticeably retarded, shaving being necessary once a week as compared to once a day before operation. His hair had become coarser and somewhat dry. These signs and symptoms, however, had shown no progression in the last two months. His mind remained perfectly clear, and he was more than usually alert. The basal metabolism had continued low, and the velocity of blood flow remained slow. There had been no appreciable change in the red cell count and the hemoglobin since operation. The

slight secondary anemia present before operation, with a red cell count of 4,330,000 and a hemoglobin of 75 per cent (Sahli), had shown little change. Six months after operation, the red cell count was 4,220,000, and the hemoglobin was 70 per cent. Successive electrocardiograms showed no change.

Comment.—This patient with rheumatic heart disease, angina pectoris and congestive failure of three years' duration showed immediate improvement corresponding to the fall in the metabolic rate. At the time of writing he showed no evidence of congestive failure and at no time had he had dyspnea, palpitation, pain in the chest or edema in spite of the fact that he had been working eight hours a day during the preceding three months. His strength had increased, and his capacity to perform work was greater than at any time during the preceding three years. In spite of the permanent lowering of the metabolic rate and the development of mild unprogressive symptoms of myxedema, he remained mentally clear, was unusually alert and was capable of concentration in a highly satisfactory manner.

A summary of the important clinical findings before and after operation in the 10 patients of this series is given in table 3.

COMMENT

Two pitfalls in accurately evaluating a clinical therapeutic measure consist in the favorable effect of suggestion and spontaneous improvement due to changes in the natural history of the condition. Throughout this investigation we have tried to reduce such errors to a minimum. The patients were separated after operation so far as possible, and particular care was exercised to avoid leading questions. Only subjects who we felt could be relied on for intelligent reports of their subjective sensations were studied. The disappearance of orthopnea and the changes in the other objective signs of congestive failure have been particularly noted, and as many quantitative measurements as feasible have been made. To make it improbable that spontaneous changes could account for the improvement in any instance, only patients whose clinical course had remained practically unchanged or steadily progressive for many months or years were chosen. They had all received medical evaluation of their condition from time to time before coming to this hospital, and previous observations in other institutions and in this hospital were carefully studied. The beneficial effect of continued rest in bed during the preoperative study and postoperative convalescence could be safely discounted in the evaluation of the efficacy of total ablation, for all of the patients had previously had much longer periods of rest with adequate medical treatment without showing significant improvement. The medical treatment of all the patients was the same after operation as before it.

THE EFFECT OF TOTAL ABLATION OF THE THYROID ON ANGINA PECTORIS

The effect of total ablation of the thyroid on angina pectoris was observed in 2 patients, W. B. and A. B. (cases 4 and 5). Definite beneficial effect after operation was noted in the patient in case 5, who had increasingly frequent attacks over a period of eighteen months. After admission to the hospital, but before operation, he was able to walk up several flights of stairs at the prevailing warm temperature of the hospital without distress. The walking of short distances on level ground in the cold outdoor, winter weather provoked attacks readily, however. We realized that the weather would be warm during his postoperative convalescence and that the absence of attacks following the operation could not be attributed to the effects of complete ablation. It was decided, therefore, to study his condition in an environment which could be accurately controlled and which could be reproduced at will any time of the year. A Barach oxygen chamber filled with room air was cooled to approximately 52 F. Before operation, the same measured amount of work under such standard conditions regularly precipitated attacks on four different days. After operation, under the same conditions, as much as six times the same amount of work was performed without attacks of angina pectoris, the exercise being finally terminated because of physical exhaustion. Careful clinical notes, determinations of the blood pressure and pulse rate and other measurements were made; these observations, as well as others, will be the subject of a forthcoming communication.

The effect of operation on angina pectoris in case 4 was more difficult to evaluate, for the incidence of the preoperative attacks had become somewhat irregular and infrequent with the onset of congestive failure. It is worthy of note, however, that the patient is now able to walk about with greater freedom; he does not suffer from dyspnea or palpitation, and he has no cardiac pain.

There are undoubtedly several types of angina pectoris, and further observations on the effect of total ablation are desirable. These are being made. The manner in which relief is afforded by removal of the thyroid gland probably involves several different, though related, mechanisms. The decreased amount of work performed by the heart, the decreased metabolism of the heart itself and the decreased sensitivity to epinephrine are some of the possible factors that are being studied.

THE EFFECT OF COMPLETE ABLATION OF THE THYROID ON THE SYMPTOMS OF CONGESTIVE FAILURE

The effect of complete ablation of the thyroid on the symptoms of congestive failure was studied in each patient except the one in case 5, who suffered only from angina pectoris. Symptoms of congestive failure had been present in this group from two to twenty-six years; signs

of congestive failure, from one to twenty-six years. The average duration of the symptoms of congestive failure was twelve years; of the signs of congestive failure, seven years. The patients in cases 1, 2, 3, 6, 8, 9 and 10 had practically no cardiac reserve after prolonged periods of adequate medical treatment with complete rest in bed, so that the ability to be up and about without symptoms or signs of congestive failure could be attributed confidently to the effects of operation. The signs of congestive failure present when the patients were admitted to this hospital were not conspicuous, for all the patients had been in other hospitals for from months to years immediately preceding entry with the exception of the patients in cases 6, 7 and 9, who had been confined in bed at home under excellent medical supervision.

These patients showed a similarity in response that was impressive. This similarity could not have been due to suggestion, for they were separated in private rooms after operation. Within from three to fourteen days after operation, each one voluntarily stated that he felt "smoothed out" or "ironed out," that the pounding of the heart had diminished or disappeared and that slight shifts of position in bed which hitherto had caused violent palpitation could be accomplished without distress. By the end of the third or fourth week the patients noticed that whereas sedatives had previously been necessary to induce sleep, they were now able to sleep soundly without medication. Subjects who formerly suffered from orthopnea found that they were more comfortable when sleeping on one or two pillows. All noticed that they were able to breathe much more easily by the end of the third postoperative week and were unaware of the action of the heart. The preoperative craving for water disappeared. Many, particularly those who were underweight, noticed increased appetite. The diet was increased in such instances, with a gain in body weight, amounting to as much as 20 pounds (9 Kg.) in the patient in case 2, who had been emaciated. In no instance was overweight permitted. On getting out of bed, from slight to moderate exertion was performed without palpitation or dyspnea. In one instance this had been impossible for as long as twelve years before operation (case 9).

These conspicuous changes in symptomatology may have been influenced to some extent by unavoidable suggestion, but the independent descriptions by each patient conformed so closely to one another and corresponded so closely to the objective findings to be detailed that one cannot fail to be impressed.

THE EFFECT OF TOTAL ABLATION OF THE THYROID ON SIGNS OF CONGESTIVE FAILURE

Each of the patients with congestive failure had edema on getting out of bed for even a brief period of each day. Up to the time of writing, each subject had been up and about the ward without sub-

jective distress and without any evidence of pitting edema or other signs of congestive failure. Râles, which were present at the bases of the lungs previous to operation, had disappeared; engorgement of the liver had lessened, as evidenced by a diminution in the size and the absence of tenderness. The ventricular rates of the patients had become steadier and had inclined to a lower level. The heart sounds had become definitely less hyperactive, and the thrust of the cardiac impulse had diminished. Less digitalis was necessary to control the ventricular rate in the patients suffering from auricular fibrillation.

Lessening of the cyanosis was evident in practically all the patients, and was conspicuous in the 2 most cyanotic patients (cases 6 and 10). In case 6, the red cell count had decreased, whereas in case 10, erythrocytosis had persisted unchanged. The more natural color of the skin after operation is probably due to the lessened engorgement of the minute vessels of the skin.

CHANGES IN CLINICAL MEASUREMENTS AFTER TOTAL ABLATION

The Basal Metabolic Rate.—There has been a significant lowering in the basal metabolic rate of each patient which, in accord with the considerations which led up to this investigation, has been closely paralleled by the clinical improvement in the circulatory condition. The decrease in the metabolic rate and the concomitant clinical improvement have occurred at various times after operation. The patients have been unaware of the results of metabolic measurements, but they always experienced their most striking improvement at the time when we found the rate lowered. Had their improvement been due to suggestion, one would have expected such improvement to be related in time to the operation rather than to reduction in the basal metabolic rate.

The Velocity of Blood Flow.—This remained greatly slowed in all the patients with a prolonged circulation time before operation. The measurements of the blood flow afford insight into the underlying mechanism of clinical improvement. In previous studies of the velocity of blood flow in patients with cardiac disease, it was found that when clinical improvement occurred under the usual medical procedure, the metabolic rate presumably remaining unchanged, the improvement was attended by an increased speed of blood flow.[31] The persistent slowing of the blood flow following operation in the cases reported in this communication indicates that the fundamental state of the circulation has not been altered. In terms of the law of supply and demand, we may say that the supply of blood has not been increased, but that the demands have been reduced to such an extent that the reduced supply is now adequate to the needs of daily life under these new circumstances.

31. Blumgart and Weiss,[3a,b] Blumgart and Weiss,[2g] Blumgart and Weiss,[5b] Blumgart, Gargill and Gilligan.[3d] Weiss and Blumgart.[5d, e]

The fact that patients who were unable to move about in bed without dyspnea before operation were able to climb the equivalent of two or three flights of stairs without discomfort after operation indicates that these patients have acquired a "cardiac reserve." There are several possible mechanisms which might bring this about. One rational explanation follows from the fact that in 7 of our patients the velocity of blood flow after total ablation of the thyroid became even slower than it was before operation. This indicates that after total ablation of the thyroid the heart does not work as hard as it showed itself capable of working before operation. The difference between the actual work done by the heart at rest after operation and the amount of work which it can do if necessary may be termed the "cardiac reserve."

These considerations may be represented diagrammatically. The diagonal line in chart 11, labeled "no congestive failure," repre-

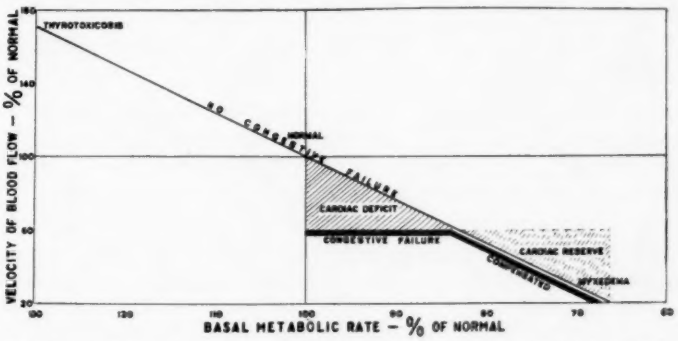

Chart 11.—Diagram showing the relationship between the velocity of blood flow and the basal metabolic rate in patients with no congestive failure and in patients with congestive failure. The line representing the relationship for patients with no congestive failure is based on previous findings.[4] The curve for patients with congestive failure is diagrammatically representative of the findings in a group of such patients before and after total ablation of the thyroid gland.

sents the relation between the velocity of blood flow and the basal metabolic rate in patients without congestive failure at various basal metabolic levels from thyrotoxicosis to myxedema. This line is plotted from actual measurements which were reported in a previous communication.[4]

The heavy horizontal line in chart 11, labeled "congestive failure," is diagrammatically representative of the relationship of the velocity of blood flow to the basal metabolic rate found in some patients with congestive failure. Such patients having 100 per cent of the normal basal metabolic rate and only 60 per cent of the normal velocity of blood flow

are decompensated persons. The degree of decompensation is represented on chart 11 by the discrepancy (read vertically) between the heavy line of "congestive failure" and the normal line of "no congestive failure." As the basal metabolic rate in such patients drops below normal following total ablation of the thyroid, the cardiac deficit becomes gradually less, the basal metabolic rate and velocity showing eventually the same relationship as in patients with similarly low basal metabolic rates and no congestive failure. At this point the slowed velocity of blood flow would be exactly sufficient for the metabolic demands of the patient at rest. As the basal metabolic rate becomes still lower, the velocity of blood flow would become proportionately slower. Seven of our patients have shown this slowing of velocity coincident with the decreasing basal metabolic rates. These patients possess, therefore, a "cardiac reserve" (chart 11), since the basal requirement placed on the heart is now less than the work that the heart is able to accomplish. The ability of the patients at the present time to undertake moderate exertion without palpitation, dyspnea and peripheral venous engorgement becomes explicable on the basis of these considerations.

The Blood Pressure.—There were no definite changes in the blood pressure following complete thyroidectomy, regardless of the level before operation.

Electrocardiographic Changes.—Changes were present in 7 patients within a few weeks after the initial fall in the metabolic rate. In 6 there was a decrease in the voltage of the Q R S complex, and in 4 a flattening of the T waves in one or more leads. The effect on premature contractions of the heart will be discussed later.

The Vital Capacity of the Lungs.—There was a decided increase in the vital capacity of the lungs in some patients, though not in all. The patients with no increase in vital capacity experienced as striking improvement in their respiratory symptoms as the others. In patients with congestive failure clinical improvement is practically always attended by an increased vital capacity of the lungs.[32] In a previous study of patients with myxedema, we observed, however, that the vital capacity of the lungs was abnormally low in spite of the absence of signs or symptoms of congestive failure.[4] Our observations in the present investigation are evidently a resultant of two opposing factors: (1) improvement in congestive failure tending to increase the vital capacity of the lungs, and (2) the development of the low metabolic rate of myxedema which tends to lower the vital capacity of the lungs.

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32. Drinker, C. K.; Peabody, F. W., and Blumgart, H. L.: The Effect of Pulmonary Congestion on the Ventilation of the Lungs, J. Exper. Med. **35**:77, 1922. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration: IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.

EXERCISE TOLERANCE TESTS

By means of exercise tests standardized for each of the 9 patients with congestive failure, it was possible to demonstrate an increased ability to perform light work following ablation of the thyroid. The exercise consisted in repeatedly mounting a staircase of 2 steps, the process being repeated until the patient was forced to stop because of fatigue and dyspnea, or until the patient had performed the amount of work specified in the standards of Master and Oppenheimer.[29] For the individual patients this work ranged between 2,700 and 3,600 foot pounds and required from twenty-one to twenty-seven trips over the staircase for its performance. Persons with normal cardiovascular systems can perform this small amount of work readily and without discomfort. On completion of the exercise the pulse and blood pressure will show a sharp rise followed by a gradual return to the previous resting level in two minutes.

Before operation three of the patients were unable to complete the work prescribed for them, whereas in 2 others the test taxed their endurance to the limit. Two of the remaining patients required more than the ninety seconds usually needed to complete the exercise. In 4 of the patients the blood pressure showed a definite and, at times, striking fall on the completion of the test, and in 3 others the exercise failed to cause any significant rise in the blood pressure until the patients had rested for from thirty to ninety seconds. Four of these patients were near collapse on completion of this small amount of work. These patients showed pallor, perspiration, a weak and thready pulse, anxiety and marked dyspnea, all of which gradually disappeared after a few minutes of rest, leaving them greatly fatigued. In every case it required from four to eight minutes for the pulse and blood pressure to return to the resting level. The patient in case 6, who had well marked mitral stenosis, showed intense cyanosis immediately following the exercise.

Following operation all of the patients showed definite improvement in the facility with which they performed the test. In order to avoid so far as possible the factor of improved muscular tone as a result of increased activity, the test was first repeated within a few days after the patient was allowed out of bed. In most instances this first repetition of the test was performed when the basal metabolic rate had shown only a moderate drop and before the maximum improvement could be expected. Nevertheless, even at this early date it was found that many patients had to be restrained to prevent them from finishing the exercise in less time than they had previously required. All of the patients noticed less fatigue and dyspnea, and several volunteered the information that exertion caused "less pounding" and that they "finished stronger."

As the metabolic rate dropped further it became apparent that the patients were able to perform the exercise with increasing ease and with less discomfort, dyspnea and fatigue. The diminution in subjective discomfort was especially striking. The five patients whose endurance had been taxed to the utmost by the test were able to do more work without embarrassment. The actual increase in work varied with the patient and with the length of time during which the basal metabolism was maintained at a low level. There was in general a slight decrease in the length of time taken for the pulse and blood pressure to return to the resting level. In only 1 instance did the blood pressure fail to show a sharp rise following the exercise, and in this person the post-operative test was performed within two weeks after the basal metabolism began to fall and within a few days after the patient had been up and around for the first time since the operation. In this person, the drop in the blood pressure which occurred was not so great as before the operation. On the basis of our experience with the other patients, it is to be expected that this patient will show further impovement in her response to exercise.

Case 1 best illustrates the changes in results of the exercise tolerance test following thyroidectomy. Three days before operation this patient performed 3,640 foot pounds of work. At that time he weighed 140 pounds (63.5 Kg.), and twenty-six trips were required to perform the work. He was unable to perform the exercise in less than two minutes. At the completion of this work he had to be helped to his chair. He was pale, perspired freely and was completely exhausted. The blood pressure, which was 104 systolic and 58 diastolic before the exercise, fell to 80 systolic and 40 diastolic. Two minutes later it reached its maximum height of 120 systolic and 56 diastolic and did not fall to the resting level until eight minutes after completion of the exercise. The pulse became thready; it rose from 88 to 136 and required four and one-half minutes to return to normal. There was marked dyspnea which did not subside for about eight minutes.

The test was repeated forty-eight days after operation. At this time the patient weighed 163 pounds (74 Kg.), and only twenty-three trips were required to perform 3,750 foot pounds of work. Throughout the exercise he had to be held back so that he would not finish the work in less than one and a half minutes. When the patient was at rest the blood pressure was 112 systolic and 70 diastolic. Following exercise it rose sharply to 160 systolic and 62 diastolic; it returned to normal in five and one-half minutes. The pulse rate rose from 92 to 140; it returned to normal in three minutes. There was very slight dyspnea for only three minutes. At the completion of the exercise the patient

experienced only slight fatigue and could have continued. On the following day he performed thirty-five trips (5,670 foot pounds) and stopped because the muscles of the thighs felt fatigued, and he began to experience slight shortness of breath. His blood pressure and pulse showed essentially the same curve as on the previous day.

THE EFFECT OF TOTAL ABLATION OF THE THYROID ON HEMOPTYSIS, HEART FAILURE PAIN AND OTHER ASSOCIATED SYMPTOMS AND SIGNS OF CONGESTIVE FAILURE

The effect of total ablation of the thyroid on hemoptysis, heart failure pain and other associated symptoms and signs of congestive failure have been striking. In patient E. W. (case 1), hemoptysis had occurred at frequent intervals for seven years. During the previous eighteen months hemoptysis had occurred as often as every day for weeks with occasional periods of freedom, the longest being two weeks. During the week immediately before operation hemoptysis occurred daily and inclined us somewhat against operation. Shortly after operation slight hemoptysis occurred once; there has been no recurrence in spite of the fact that the patient had been up and about the hospital the entire day for several weeks and in spite of his recent return home, where he has been active though not yet at work. The patients in cases 2, 6 and 8 likewise had suffered from hemoptysis before entry, though so irregularly that the absence of hemoptysis over the comparatively short postoperative period cannot be considered significant.

One of the most striking changes in patients with congestive failure has been the disappearance of pain in the chest. The patient in case 1 had suffered for five years from transient pains and aches referable to the precordium, sternum, neck, shoulders and arms. The patient in case 2 had pain in the chest anteriorly; the one in case 3 had suffered from a sense of thoracic compression; the one in case 6 had noted localized precordial pain; the one in case 8 had precordial pain which radiated to the left shoulder, and the patient in case 9 had been troubled by pain in the region of the left nipple whenever she had exerted herself during the previous three years. These sensations had been so constant that the patients had learned to minimize and practically ignore them. Only on the disappearance of the pains did some of the patients realize how constant and discomforting the symptoms had been. In all of these persons the symptoms disappeared coincident with a lowering of the basal metabolic rate; they did not recur even after an amount of exercise which had been impossible for many years.

The disappearance of premature contractions of the chambers of the heart has been interesting to note in cases 3, 5 and 8. In case 5, ventricular premature impulses which were present before operation were not observed after operation. In cases 3 and 8, the premature auricular

impulses which were present before operation disappeared after operation, when the basal metabolic rate was low. In case 3, the premature beats recurred when thyroid medication was given and disappeared again after omission of the drug, when the metabolic rate returned to its previously low level. These observations make it conceivable that attacks of paroyxysmal auricular tachycardia, otherwise uncontrollable, may be favorably affected by total ablation of the thyroid.

THE EFFECT OF TOTAL ABLATION OF THE THYROID ON PAROXYSMAL DYSPNEA

The therapeutic effect of total ablation of the thyroid on attacks of paroxysmal dyspnea has been less encouraging than in the other types of cardiovascular disease. The patient in case 4 had previously suffered from such attacks and felt entirely well after operation. The incidence of these attacks before operation was too irregular to warrant placing much significance on their absence during the relatively short postoperative period. The patient in case 7, on the other hand, had suffered from repeated attacks for many weeks before operation, and we were encouraged by the absence of attacks after operation and the disappearance, at the same time, of signs and symptoms of mild congestive failure. According to the concept that paroxysmal dyspnea is due to a relative diminution in the output of the left ventricle,[33] we hoped that the decreased work of the heart at a low metabolic rate might obviate acute weakening of the left chambers of the heart. It is possible, however, that acute exacerbations of extremely high blood pressure, such as occurred in this case, may place too great a burden on the left ventricle. We cannot be certain of this mechanism, however, for while blood pressure readings were taken within a few minutes of the onset of the attack and exceeded the limit of the top of the mercury manometer column, i. e., 300 mm., we do not know whether the elevation in blood pressure actually preceded the attack. It is possible that after thyroidectomy a disproportionate output of the two ventricles may also exist at a lower level and may amount to less than that at the previous normal metabolic level. In any event, further experience is necessary in order to evaluate the benefit that may be derived from thyroidectomy in this condition, and more prolonged rest in bed after operation probably is indicated. The disappearance of all signs of congestive failure and the absence of attacks for three weeks make it seem possible that the treatment may be attended with greater success in patients afflicted less severely and with less elevated blood pressure.

33. Weiss, S., and Robb, G. P.: The Mechanism and Treatment of the Paroxysmal Dyspnea and Asthma Associated with Heart Disease, New England J. Med. **205**:1172, 1931; The Treatment of Cardiac Asthma, M. Clin. North America **16**:961, 1933.

THE DEVELOPMENT OF THE SIGNS AND SYMPTOMS OF CLINICAL MYXEDEMA AFTER TOTAL ABLATION OF THE THYROID

The development of the signs and symptoms of clinical myxedema has been carefully observed. With the reduction in the basal metabolic rate all patients have felt calmer and less nervous. The uniformity with which patients have used the terms "smoothed out" and "ironed out" has been interesting. The heart rate has tended to be lower; the respiratory rate has become slightly slower and, in the patients subject to fluctuations, much steadier. The temperature has not changed perceptibly. Within from four to six weeks the skin has become somewhat paler, has acquired a slightly yellowish tint and has become somewhat dry. After the metabolic rate decreased to minus 30 per cent, some patients complained of coldness of the feet and required more blankets. Several patients who formerly shaved once daily required a shave only every several days; the patient in case 11 (case 3 of the previous communication) now shaves but once a week.

Each of us has been impressed with the fact that in every patient, instead of the mental lethargy of myxedema, unusual brightness and alertness have been present during the months that they have been studied. Each of the patients has spontaneously commented on this change. This is probably due to the fact that these patients compare their postoperative mental condition with the grogginess of circulatory failure, and that mental lethargy is a manifestation of more advanced myxedema.

Measurements of the heart from roentgenograms taken at a distance of 7 feet have not shown any postoperative changes to date. Particular attention has been devoted to the appearance of evidence of the signs or symptoms of the so-called myxedema heart.[34] Assmann,[35] Fahr[36] and others have described a form of myocardial failure characteristic of myxedema which is alleviated only by thyroid therapy. On the other hand, Means, White and Krantz,[37] in a study of 48 patients with myxedema, encountered but 1 such case. In 162 cases Willius and Haines[38] found no evidence of heart failure or of organic cardiovascular disease that could be attributed to the myxedema. Christian[39] similarly stated that he had never observed the condition.

34. Zondek, H.: Das Myxödemherz, München. med. Wchnschr. **65**:1180, 1918.

35. Assmann, H.: Das Myxödemherz, München. med. Wchnschr. **66**:9, 1919.

36. Fahr, George: Myxedema Heart, J. A. M. A. **84**:345 (Jan. 31) 1925.

37. Means, J. H.; White, P. D., and Krantz, C. I.: Observations on the Heart in Myxedema, Boston M. & S. J. **195**:455, 1926.

38. Willius, F. A., and Haines, S. F.: The Status of the Heart in Myxedema, Am. Heart J. **1**:67, 1925.

39. Christian, H. A.: Myocardial Disturbances Due to Abnormal Thyroid Function and Their Management, Pennsylvania M. J. **32**:70, 1928.

More numerous examples of the opposite course of events are available, namely, thyroid therapy precipitating circulatory insufficiency rather than alleviating it. Swan [40] has reported the case of a patient with myxedema in whom fibrillation of the auricles appeared whenever thyroid substance was administered, the heart action returning to normal whenever the drug was discontinued. Read [41] and Means, White and Krantz [37] have reported cases in which the administration of thyroid substance caused attacks of angina pectoris. Sturgis and Whiting [42] and Pratt and Morton [43] observed patients in whom, on each attempt to give thyroid gland, the signs of congestive failure appeared. Christian [44] has laid particular emphasis on the danger of increasing the heart action of certain myxedematous patients by thyroid medication.

In a recent review of hypothyroid heart disease, Means described the enlarged heart shadow occurring in almost all the cases studied at the Massachusetts General Hospital and shrinkage in the transverse diameter following thyroid therapy.[45] Should any untoward effects of myxedema on the heart become manifest in our cases, some elevation of the metabolic rate by thyroid substance may be advisable.

MEDICAL MANAGEMENT OF THE OPERATIVE COURSE

All of the patients were observed for periods ranging from two weeks to two months before operation. While we were studying the extent of their cardiac reserve and making an appraisal of their general medical condition, the physical condition was improved to the fullest possible extent in order to minimize the risk of operation.

Several days before operation the patients received a therapeutic dose of morphine sulphate so that we could be certain that the drug caused its characteristic sedative effect. In several instances the drug had a stimulating effect, causing insomnia, excitement and other conditions; barbituric acid derivatives were employed in such subjects immediately before operation.

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40. Swan, J. M.: A Case of Auricular Fibrillation Occurring During the Administration of Thyroid Substance, Ann. Clin. Med. **3**:311, 1924.

41. Read, J. M.: Treatment of the Cardiac Disturbances Due to Thyroid Disease, J. A. M. A. **89**:493 (Aug. 13) 1927.

42. Sturgis, C. C., and Whiting, W. B.: The Treatment and Prognosis in Myxedema, J. A. M. A. **85**:2013 (Dec. 26) 1925. Sturgis, C. C.: Angina Pectoris as a Complication in Myxedema and Exophthalmic Goiter, Boston M. & S. J. **195**:351, 1926.

43. Pratt, G. P., and Morton, H. B.: Management of the Circulation in Myxedema, Am. J. M. Sc. **173**:274, 1927.

44. Christian, H. A.: The Heart and Its Management in Myxedema, Rhode Island M. J. **8**:109, 1925.

45. Means, J. H.: Hypothyroid Heart Disease, New England J. Med. **208**: 541, 1933. Lerman, J.; Clark, R. J., and Means, J. H.: The Heart in Myxedema: Electrocardiograms and Roentgen-Ray Measurements Before and After Therapy, Ann. Int. Med. **6**:1251, 1933.

Immediately before and throughout the operation the state of the cardiovascular system was carefully observed, and occasionally, when indicated, additional digitalis was given. Although various general anesthetics were used at the beginning of this investigation, we have found gas-oxygen anesthesia the most satisfactory one at our disposal. In 2 patients a small amount of ether was employed as a supplementary anesthetic.

Following operation, sedatives were again administered when necessary. Edema was present in some of the patients, and in these cases hypodermoclyses were not given. From 500 to 1,000 cc. of physiologic solution of sodium chloride was given subcutaneously to other patients. For some patients who drank fluids shortly after the operation without discomfort or difficulty, parenteral administration of fluids was considered unnecessary.

We have not encountered serious parathyroid tetany. All of the patients were instructed to report to the nurse on duty, or to us, the onset of numbness, tingling, "queer sensations" and other symptoms, and were also questioned several times daily. During the first week of the postoperative course, repeated measurements of the calcium content of the blood were made, and tests were carried out at intervals of from three to six hours for Chvostek's and Trousseau's signs. Such signs became evident in 2 patients. From 2 to 8 cc. of a 35 per cent solution of calcium chloride orally from four to six times a day, and 0.5 cc. of viosterol, 250 D, four times daily, have controlled the symptoms and signs. Decreasing amounts have been given without recurrence of the symptoms or signs, and it appears possible that medication may become unnecessary. A quart of milk was also included in the diet. Parathyroid extract-Collip was not employed except in 1 patient. A single dose was given by the nurse, according to our standing orders for the night when Chvostek's and Trousseau's signs became evident.

We have not administered compound solution of iodine to any of our patients before operation, for iodine does not lower the basal metabolic rate in patients with normal thyroids and has been described as activating quiescent adenomas.

The greatest danger in this operation, we believe, is injury to the recurrent laryngeal nerves.[46] Laryngoscopic examinations were made before, during and after the operations through the cooperation of Dr. Louis M. Freedman. Direct laryngoscopic examination was made after complete ablation of one-half the thyroid gland. Though it has

46. Berlin, D. D., and Lahey, F. H.: Dissections of the Recurrent and Superior Laryngeal Nerves (The Relation of the Recurrent to the Inferior Thyroid Artery and the Relation of the Superior to Abductor Paralysis), Surg., Gynec. & Obst. **49**:102, 1929.

not been necessary thus far, we intend to terminate the operation at this stage should the recurrent laryngeal nerve be affected. The operation may be completed at a later date if the nerve regains its function.

Immediately after operation one of the patients showed a recurrence of râles and rhonchi over the dependent portions of both lungs. In some patients there was a postoperative reaction with a temperature of 103 F. and corresponding elevations in the cardiac and respiratory rates. Discomfort was readily controlled by sedatives, and the condition of none of the 10 patients warranted grave concern. Approximately half of the patients of this series showed no appreciable postoperative rise in the temperature or the pulse and respiratory rates.

The degree of local discomfort varied considerably; some patients talked immediately after operation and took solid food and liquids without discomfort, while a few complained of local soreness in the region of the wound and had pain on swallowing during the first few days, which gradually disappeared by the fifth or sixth postoperative day. The surgical details of the operative procedure and the precautions to be observed have been described in a previous communication.[47]

OPERATIVE MORTALITY

Besides the 10 cases recorded in this communication, 1 postoperative death occurred in the present series thirty-six hours after thyroidectomy, owing to pulmonary complications. This patient was 62 years of age and had suffered from congestive failure for many years. The diagnosis was generalized arteriosclerosis and advanced aortic stenosis and insufficiency. The patient showed no stridor after operation, but was troubled by the accumulation of considerable mucus. Bronchopneumonia resulted and was evidently caused by a combination of excessive secretion of mucus and injury of the recurrent laryngeal nerve, which made it difficult for the patient to cough up the accumulated mucus. This patient was the only one of the series on whom tracheotomy was performed. In retrospect, we are inclined to believe that tracheotomy should be employed early, in accord with the experience of Crile.[48] Including the patients in the cases reported in the previous communication, 16 patients have been operated on with 2 postoperative deaths. The first death was also due to postoperative pulmonary complications, with mediastinitis possibly as a result of the opening up of the fascial planes of the

47. Berlin, D. D.: The Therapeutic Effect of Thyroidectomy on Congestive Heart Failure and Angina Pectoris in Patients with No Clinical or Pathological Evidence of Thyroid Toxicity: II. Operative Technic, Am. J. Surg. **21**:173 (Aug.) 1933.

48. Crile, George, and others: Diagnosis and Treatment of Diseases of the Thyroid Gland, Philadelphia, W. B. Saunders Company, 1932.

lower part of the neck. In subsequent operations the lower portion of the neck has been exposed as little as possible, and this complication has not been encountered.

When one considers the poor physical condition of our subjects and their lack of cardiac reserve, the mortality of the operation to date has been fortunately low. Complications which proved fatal in these cases might have been withstood by patients in better condition. One patient who decided not to have the operation died three days after leaving the hospital, and in 2 others hemiplegia developed a few days before the date planned for operation. With increasing experience, we believe that the mortality rate of this operation can, nevertheless, be further reduced.

THE ADVANTAGES AND DISADVANTAGES OF TOTAL ABLATION OF THE THYROID

Total ablation of the thyroid was performed on all of the patients in this series. The reasons for so doing have been discussed in a previous communication.[1] Subsequent experience has reenforced our belief that this is the operation of choice, for in each of the 11 patients operated on, a conspicuous lowering of the basal metabolic rate has, up to the time of writing, been maintained. In contrast to this, extensive subtotal removal of the thyroid, performed on 2 patients with congestive failure, resulted in only temporary lowering of the basal metabolic rate,[1] and both patients have relapsed to their preoperative clinical condition. In 1 patient (case 2 of the preceding series) an attempt was made subsequently to remove the remaining fragments of thyroid tissue, without success. Irradiation therapy in this case, as well as in others to be reported, has likewise been attended with uncertain results. Subtotal thyroidectomy may at times be attended by improvement, but the uncertainty of beneficial results and the further uncertainty of being able to remove the residual thyroid tissue at a subsequent operation contraindicate this procedure.

In contrast to the clinical course of the 2 patients on whom subtotal thyroidectomy was performed has been the clinical course of patient G. F., who was the first person on whom total ablation of the normal thyroid was performed, six months ago.[1] This patient had been confined to bed for more than two years because of congestive failure. During that time he continually suffered from dyspnea, orthopnea and transient attacks of pain in the chest. Even turning over in bed or combing his hair caused violent palpitation. Râles at the bases of the lungs, pitting edema of the legs and hepatic enlargement were constantly present.

The results of ablation of the thyroid four weeks after operation have already been reported.[1] At that time the basal metabolic rate had reached a level of minus 28 per cent, and coincident with this there was

striking improvement in the clinical condition. The preoperative thirst, palpitation, dyspnea, orthopnea, cyanosis, edema and hepatic tenderness disappeared, and he became free from pain in the chest.

Six months have elapsed since the operation was performed, and during this time the low metabolic rate and the clinical improvement have been maintained. During the past three months the patient has been working forty-eight hours a week and has been on his feet practically the entire day. With the increase in activity he has gradually gained muscular strength, so that he is able to walk as far as a mile without dyspnea or fatigue. At no time has he noticed cough or edema. He sleeps soundly with only one pillow.

Signs of mild hypothyroidism have developed. There is a yellowish tinge to the skin. The patient now shaves but once a week, whereas formerly this was a daily necessity. His feet feel cold, so that he wears woolen socks in May. He shows none of the mental slowing, however, which is usually associated with myxedema.

From a state of uncomfortable chronic invalidism the patient has been restored not only to moderate activity without discomfort, but to a condition of occupational usefulness.

This communication presents only the early results following operation. The patient in case 5 was unable to work because of angina pectoris, and the other patients were completely incapacitated and forced to remain in bed practically all the time. To date, we may say that months of effective life have been added to the lives of these patients. In effect, we seem to have extrapolated backward on the life history curve of their disease. In patients with rheumatic valvular disease, the obstruction or insufficiency of the valves has not been affected, nor has the level of the blood pressure been altered in patients with hypertension. The underlying mechanism of paroxysmal dyspnea does not seem to be completely obviated. Appraisal of the ultimate value of this procedure must, therefore, await continued study of these patients and other patients, who we hope will be observed by other investigators. The broad general considerations of the supply of blood and metabolic demand which underlie this investigation may be applicable to other fields. One of our patients suffered from Paget's disease, and we are observing his condition carefully. Patients suffering from other metabolic disorders, such as diabetes mellitus, may conceivably benefit from a reduced metabolism. The improvement shown by 1 of our patients with bronchial asthma is likewise suggestive. Whether a reduced metabolic rate will affect chronic infections, such as tuberculosis, favorably or adversely cannot be foretold with certainty. These phases of the problem are being studied.

It is hoped that ultimately operation will be unnecessary to produce a low metabolic rate. Many studies have been made on antithyroidal substances, and comparatively recent reports give hope that the administration of such substances may cause lowering of the metabolic rate.[49]

Because of the uncertainty as to the ultimate duration of the beneficial results, we feel that this operation should be undertaken at the present time only on patients with congestive failure or angina pectoris in whom the operative risk is fair and in whom all other medical procedures have been employed without the desired therapeutic results. Patients with active coronary disease, active infection, repeated pulmonary infarctions, vascular accidents or rapidly progressive syphilitic cardiovascular disease are probably unfavorable subjects.

SUBSEQUENT NOTE: Since this paper has been in press, each patient has shown further improvement. Some patients who at the time of writing were up and about without distress are now able to walk several miles daily. The basal metabolic rates have remained low and the velocity of blood flow, slow.

SUMMARY AND CONCLUSIONS

1. The early therapeutic results following total ablation of the thyroid in 10 patients with congestive heart failure or angina pectoris are reported.

2. The subsequent clinical course of the first patient who was treated by this procedure, six months ago, and whose case was described in a previous communication is given.

3. The clinical observations which provided the rationale for this procedure are given, and the historical background is reviewed.

4. Attacks of angina pectoris, which were present in 2 patients before operation, have not recurred since complete thyroidectomy. In 1 of these patients, before operation the same measured amount of work under standard conditions regularly precipitated attacks. After operation, under the same conditions, as much as six times the same amount of work was performed without attacks of angina pectoris, the exercise being finally terminated because of physical exhaustion.

5. Seven of the 9 patients with congestive failure had practically no cardiac reserve after prolonged periods of adequate medical treatment

49. Anselmino, K. J., and Hoffmann, F.: Darstellung, Eigenschaften und Vorkommen einer antithyreoiden Schutzsubstanz aus Blut und Geweben, Klin. Wchnschr. **12**:99, 1933. Romeis, B.: Untersuchungen über die Wirkung des Thyroxins: III. Ueber die Zerstörung der spezifischen Wirkung des Thyroxins durch die Einwirkung von Blut in vivo und in vitro, Biochem. Ztschr. **141**:500, 1923.

with complete rest in bed, so that the ability to be up and about without symptoms or signs of congestive failure could be attributed confidently to the effects of operation.

6. During the period of observation of three to six months that have elapsed since operation, all of the patients have shown conspicuous improvement. They have been able to undertake from slight to considerable exertion without the development of palpitation, dyspnea or any signs of congestive failure. The preoperative craving for water has disappeared.

7. The basal metabolic rate of each patient has shown a significant and persistent lowering which has paralleled the most striking improvement.

8. The velocity of blood flow has become slower in 7 patients, indicating that the heart is required to do less work under the new postoperative condition than it was able to accomplish when the metabolic rate was normal. These patients may therefore be regarded as being in possession of a definite "cardiac reserve."

9. The vital capacity of the lungs showed a decided increase in some patients, though not in all. The significance of these findings is discussed.

10. By means of exercise tests standardized for each of the 9 persons with congestive failure, an increased ability to perform light work after operation has been demonstrated.

11. Frequently recurring hemoptysis and pain in the chest have disappeared following operation.

12. One patient who suffered from paroxysmal dyspnea showed improvement for three weeks following operation. On the twenty-second day he suffered from an attack of acute pulmonary edema during which he died. Further experience is necessary to evaluate the possible benefit to be derived from thyroidectomy in this condition, and operation should be undertaken in this type of cardiovascular disease with extreme caution.

13. Following operation patients have had slight dryness of the skin, increased sensitivity to cold, slow growth of hair and a lower heart rate. Thyroid substance has not been given except for short periods to 2 patients; in the others, it has not been indicated thus far.

14. The medical management of the operative course is described.

15. In 1 patient with congestive failure who had suffered from continuous attacks of bronchial asthma since childhood, no severe attacks have occurred since operation. The possible beneficial effects of the procedure in other conditions are discussed.

16. Because of the inevitable uncertainty as to the ultimate duration of the beneficial results, we feel that this operation should be undertaken at the present time only on patients with congestive failure or angina pectoris, in whom the operative risk is fair and in whom all other medical procedures have been employed without the desired therapeutic results. Patients with active coronary disease, active infection, vascular accidents, repeated pulmonary infarctions or rapidly progressive syphilitic cardiovascular disease are probably unfavorable subjects.

CLINICAL STUDIES OF RESPIRATION

II. INFLUENCE OF DETERMINATION OF BASAL METABOLISM ON RESPIRATORY MOVEMENTS IN MAN, AND EFFECT OF THESE ALTERATIONS ON CALCULATED BASAL METABOLIC RATE

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In a preceding paper,[1] a plethysmographic method was described for the study of the respiratory movements in man, and it was shown that in repose the expiratory position of the chest is usually, though not necessarily, almost constant, and that it may be altered by a change in the position of the body, by muscular activity or by speech.

The alteration that accompanied muscular activity appeared to be due to a psychic or reflex mechanism. In order to investigate the latter factors further, the influence of the determination of basal metabolism on the respirations was studied.

When the basal metabolic rate is determined, a face mask or a mouthpiece and nose-clip are used in connecting the subject's lungs to the spirometer. The application of this apparatus produces a psychic or reflex reaction in some subjects, and the respirations are materially altered. It was noted by Carpenter,[2] in comparing the different methods for the determination of gaseous exchange, that there was a distinct alteration of the respiratory movements in some subjects.

METHOD

Thirty-four studies were made on three normal members of the laboratory staff and twenty patients from the hospital wards. A continuous record of the respiratory movements was obtained before, during and after the metabolic test.

With the patient in the postabsorptive state and quieted by a rest period of from thirty to forty-five minutes, the respirations were recorded for from fifteen to twenty minutes by the plethysmographic method. Then without interruption of the

From the Lilly Laboratories for Clinical Research, Indianapolis City Hospital, and the Department of Medicine, Indiana University.

1. Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respiration: I. A Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities on the Expiratory Position of the Chest in Man, Arch. Int. Med. **52**:44 (July) 1933.

2. Carpenter, T. M.: A Comparison of Methods for Determining the Respiratory Exchange of Man, Washington, D. C., Carnegie Institution, 1915, pub. no. 216.

plethysmographic record the gaseous exchange was determined by the closed circuit method. The carbon dioxide was absorbed and weighed.

Each metabolic study was divided into two periods of six minutes each. The mouthpiece and nose-clip were not removed, but the expired air was diverted to other absorptive containers, and oxygen, when needed, was added to the spirometer.

The plethysmographic record was continued for from ten to thirty minutes after the metabolic study had been completed.

TABLE 1.—*Alterations in Respiratory Movements During Determination of Basal Metabolic Rates in Twenty-Three Persons*

Case	Diagnosis	Test No.	Change in Rate	Change in Amplitude	Change in Expiratory Position	Change in Ventilation	Rhythm	Change in Rhythm	Previous B.M.R.
1	Normal	1	0	Inc.	0	Inc.	Reg.	0	Yes
		2	0	Inc.	0	Inc.	Reg.	0	
2	Normal	1	0	Inc.	0	Inc.	Reg.	0	Yes
		2	0	Inc.	0	Inc.	Reg.	0	
3	Normal	1	Dec.	Inc.	Inc.	Inc.	Und.	Reg.	No
4	Psychoneurosis	1	0	Inc.	0	Inc.	Reg.	0	Yes
5	Psychoneurosis	1	0	Inc.	0	Inc.	Reg.	0	Yes
		2	0	Inc.	0	Inc.	Reg.	0	
6	Psychoneurosis	1	0	Inc.	0	Inc.	Reg.	0	Yes
		2	Inc.	Inc.	0	Inc.	Reg.	0	
7	Effort syndrome	1	0	0	Inc.	(?)	Und.	0	Yes
		2	0	0	Inc.	(?)	Und.	0	
8	Polycythemia	1	0	Inc.	0	Inc.	Und.	Reg.	Yes
		2	0	Inc.	0	Inc.	Und.	0	
		3	0	Inc.	0	Inc.	Reg.	0	
9	Hyperthyroidism	1	Dec.	Inc.	0	Inc.	Reg.	0	Yes
		2	Dec.	Inc.	0	Inc.	Reg.	0	
10	Hyperthyroidism	1	Inc.	Inc.	0	Inc.	Sig.	0	No
11	Hyperthyroidism	1	0	Inc.	0	Inc.	Reg.	0	No
12	Myxedema	1	0	Inc.	0	Inc.	Reg.	0	No
		2	0	Inc.	0	Inc.	Reg.	0	
13	Colloid goiter	1	0	Inc.	0	Inc.	Sig.	0	Yes
14	Pernicious anemia	1	0	Inc.	0	Inc.	Reg.	0	No
		2	0	Inc.	0	Inc.	Reg.	0	
15	Pernicious anemia	1	0	Inc.	0	Inc.	Und.	0	No
16	Pernicious anemia	1	0	Inc.	0	Inc.	Reg.	0	No
17	Pernicious anemia	1	0	Inc.	0	Inc.	Reg.	0	No
18	Diabetes (mild)	1	Inc.	Inc.	Inc.	Inc.	Reg.	0	No
19	Rheumatic heart disease (decompensated)	1	0	Inc.	0	Inc.	Reg.	0	Yes
20	Myelogenous leukemia	1	Dec.	Inc.	0	Inc.	Reg.	0	No
		2	Dec.	Inc.	0	Inc.	Reg.	0	
21	Enuresis	1	Dec.	Inc.	0	0	Reg.	0	No
22	Pregnancy	1	0	Inc.	0	Inc.	Und.	0	No
23	Pulmonary tuberculosis	1	0	Dec. and Inc.	Inc. and Dec.	Dec. and Inc.	Reg.	0	Yes

No change is indicated by 0; an increase, Inc.; a decrease, Dec.; regular respiration, Reg.; undulatory respiration, Und., and sighing respiration, Sig.

INFLUENCE OF THE DETERMINATION OF THE BASAL METABOLISM ON THE RESPIRATORY MOVEMENTS

The respiratory movements were altered during the metabolic study in all the subjects. The results are given in table 1.

The respiratory rate was increased in three subjects. During a previous study there had been no change in rate in one of these subjects.

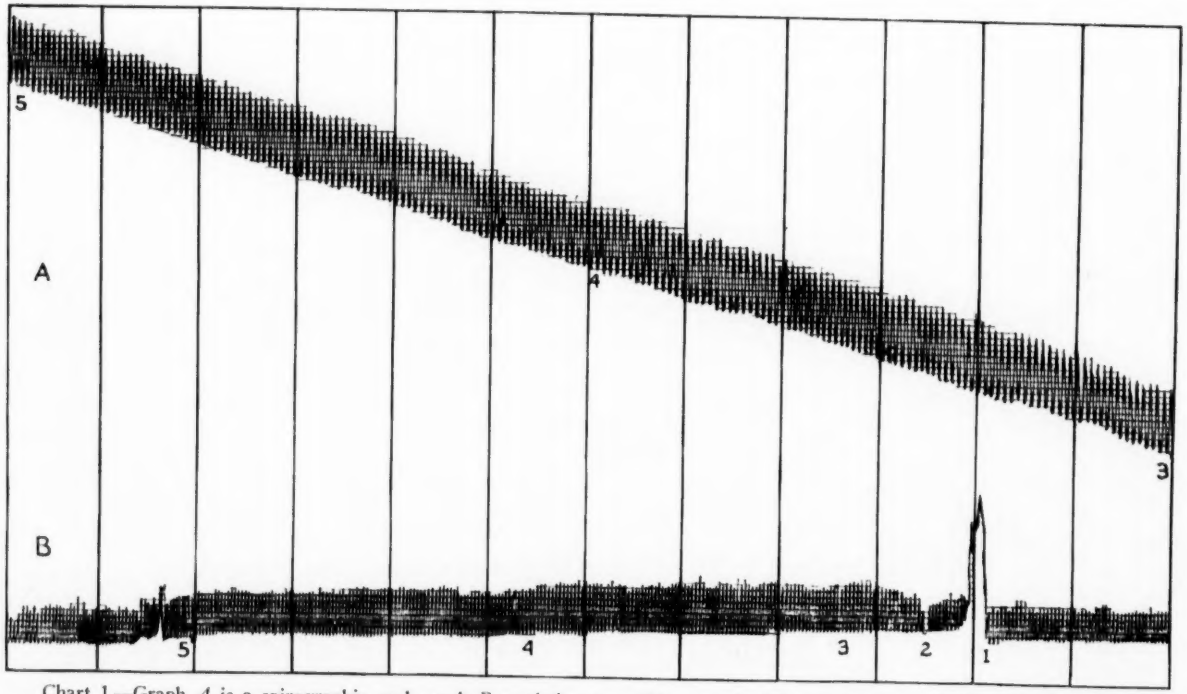

Chart 1.—Graph *A* is a spirographic, and graph *B*, a plethysmographic, record. The graphs are read from right to left, and the down stroke indicates expiration. At 1 the mouthpiece was inserted; at 2 the nose-clip was applied; at 3 the expired air was diverted to weighed absorptive containers; at 4 it was diverted to the second weighed absorptive containers, and at 5 the metabolic test was discontinued.

The rate was decreased in four subjects during six examinations. It was unchanged in seventeen subjects during twenty-five examinations.

The amplitude of the respiratory movements increased in twenty-one subjects during thirty-one of the thirty-four examinations. The two extremes of change in amplitude are shown in charts 1 and 2. The amplitude decreased slightly in subject 23 during the first period of study, and increased slightly during the second period. There was no change in amplitude in subject 7 during two examinations.

The rhythm was altered in two subjects during two examinations. Before the metabolic determinations were made, the respiratory movements in seven examinations of five subjects were undulatory. This

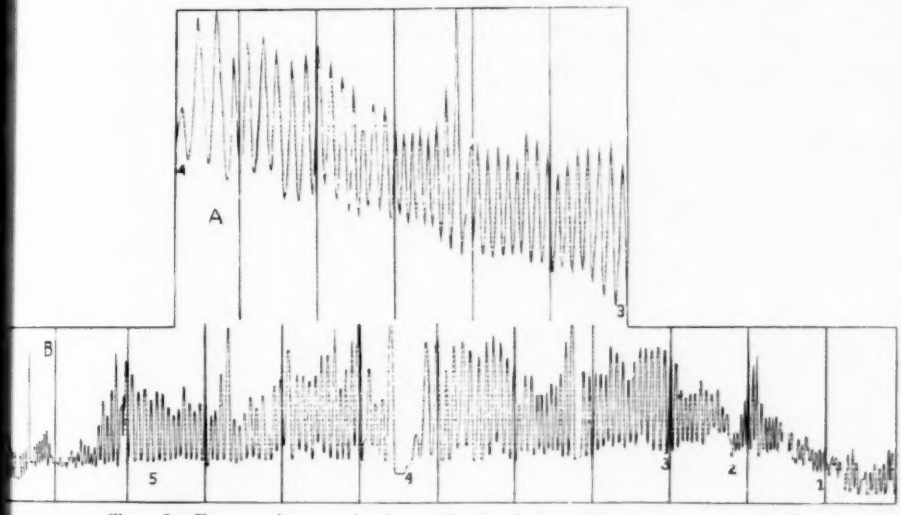

Chart 2.—Extreme increase in the amplitude of the respiratory movements and in the expiratory position of the chest after application of the nose-clip.

character of the respiratory movements disappeared in two subjects during examinations, but reappeared in one of them during a subsequent examination. It persisted in the remaining three. Respirations with sighing were present in two subjects and persisted during the metabolic test. The rhythm was unaltered during the remaining twenty-five examinations.

The expiratory position of the chest increased during the metabolic determination in five examinations of four subjects. The increase began in each subject when the mouthpiece was inserted and in three instances the position remained constantly elevated after the nose-clip was applied. At the end of the metabolic test, the expiratory volume of the chest returned to the previous level, as shown in charts 2 and 3.

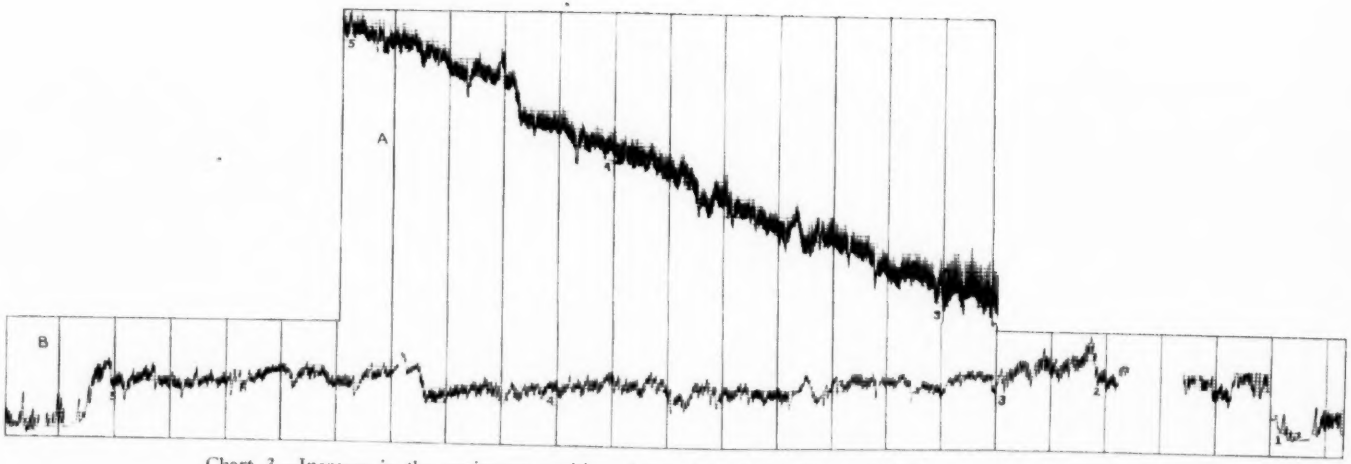

Chart 3.—Increase in the expiratory position of the chest during determination of the metabolic rate.

In one subject the expiratory position continued to increase during the first period of the metabolic study, but decreased during the second period, as shown in chart 4.

The primary function of external respiration is the proper ventilation of the lungs, that is, to keep sufficient oxygen available in the alveolar air and, by discharging the carbon dioxide, to maintain the proper tension. Alterations in the rate or in the amplitude of the respiratory movements therefore do not indicate alterations of the respiratory function unless they affect the rate of ventilation of the lungs. The relative volume of ventilation was determined from the plethysmograms by adding the individual inspiratory volumes for several minutes before the test, and comparing the sum with that of the inspiratory volumes for a similar time during the test. So long as the expiratory position of the chest remained constant, the respiratory quotients were approximately normal when the rate of ventilation was normal or slightly increased, and elevated when this was moderately or markedly increased. The ventilation was increased in thirty examinations. In twenty-two instances it was increased by a change in amplitude alone; in five it was increased because of an increase in amplitude in spite of a decrease in rate; in two subjects the increase in ventilation accompanied an increase in both amplitude and rate. Another showed an increase in ventilation with increases in amplitude, rate and expiratory position. During one study the ventilation was not changed, since, although the amplitude increased, the rate decreased proportionately.

The ventilation during three examinations in subjects 7 and 23 is difficult to appraise. In subject 23 the rate was not altered, the amplitude decreased slightly, the expiratory position of the chest increased markedly during the first period of the metabolic study, and the amplitude increased slightly with a reduction in the expiratory position without change in rate during the second period (chart 4). During the first period oxygen was stored in the lungs, and carbon dioxide was retained, owing to an increase in the expiratory volume of the chest. Some oxygen which was not utilized was therefore removed from the spirometer, and some carbon dioxide which was produced remained in the lungs and was not measured. This combination of circumstances led to a respiratory quotient of 0.37 during the first period. In the second period, the volume of the chest decreased, the stored oxygen was utilized, and the accumulated carbon dioxide was exhaled and measured, so that a respiratory quotient of 1.77 was obtained. However, the respiratory quotient for the combined period was 0.83, which indicated that the changes in ventilation equalized each other. The changes in this subject are admittedly extreme, and the appearance of the spirographic tracing would indicate that the test was unsatisfactory; but the same type of change in the expiratory position of the chest, if

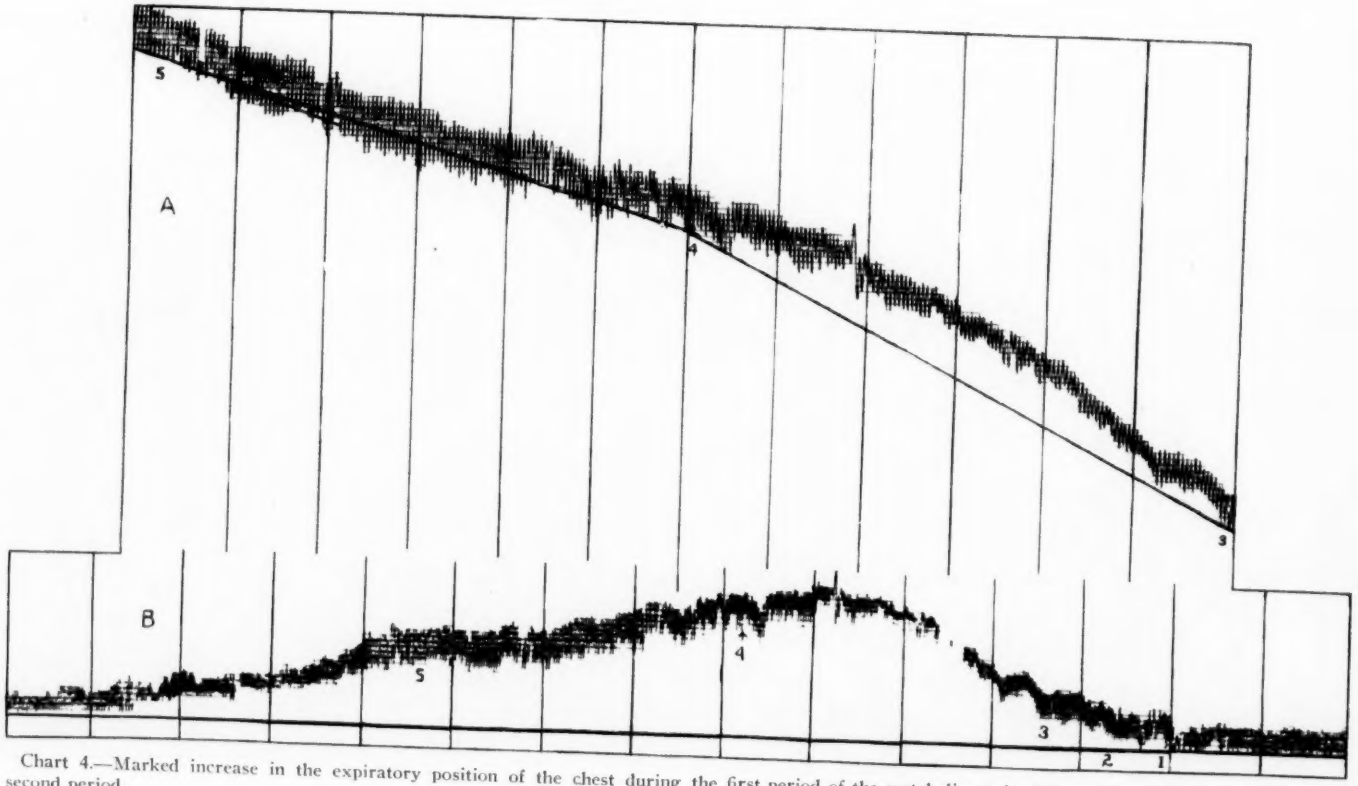

Chart 4.—Marked increase in the expiratory position of the chest during the first period of the metabolic study, followed by a decrease during the second period.

less marked, might easily go unrecognized were it not for the plethysmographic record. Subject 7 exhibited an increase in the expiratory position of the chest without alteration in the rate or amplitude and maintained a low respiratory quotient throughout the test. The respiratory quotient in the second period was lower than that in the first, and on both occasions was below 0.7.

In the group of normal subjects, two who were trained reacted by an increase in amplitude alone. The third, who was familiar with the procedure but who had never been a subject, showed an increase in amplitude and expiratory position of the chest, with a decrease in rate and a change in rhythm.

The basal metabolic rate of eleven of the patients had been determined previously; some of them showed as marked alterations in the respiratory movements as patients not familiar with the procedure. The same subject may show a different reaction during successive tests, as illustrated by patients 6 and 8 (table 1). Patient 6 showed no change in rate during one examination, but demonstrated an increase in a subsequent test. Patient 8 showed a change in rhythm during one test and none during a subsequent study. Patient 7 showed a variety of irregularities; the spirographic tracings (chart 5) are obviously too irregular to be of value in determining oxygen consumption. The greatest changes were in amplitude and in the expiratory position of the chest. Chart 3 shows simultaneous spirographic and plethysmographic records for this patient. Variations in the expiratory position of the chest are present, but the position is approximately the same at the end as at the beginning. The measured oxygen consumption would therefore appear to be reliable, except that irregular breathing entails more muscular effort than normal, quiet breathing. This patient exhibited changes in the respiratory movements whenever his attention was directed to his breathing.

Chart 4.—Marked increase in the expiratory position of the chest during the first period of the metabolic study, followed by a decrease during the second period.

THE INFLUENCE OF THE ALTERATIONS OF THE RESPIRATORY MOVEMENTS ON THE CALCULATED BASAL METABOLISM

The influence of alterations in the respiratory movements on the results of the basal metabolic tests was also studied. Increases in ventilation due to changes in the rate or the amplitude, or both, do not materially alter the consumption of oxygen, as Carpenter has shown. In five studies on four subjects as well as in one subsequent observation there was a significant change in the expiratory position of the chest during the determination of the basal metabolic rate. Such an alteration of the respiratory movements may cause the apparent basal metabolic rate to be increased or decreased. Should an increase in the expiratory position occur before the test, with a decrease during the test, as evidently was the case with Carpenter's [2] subject who added gas to the

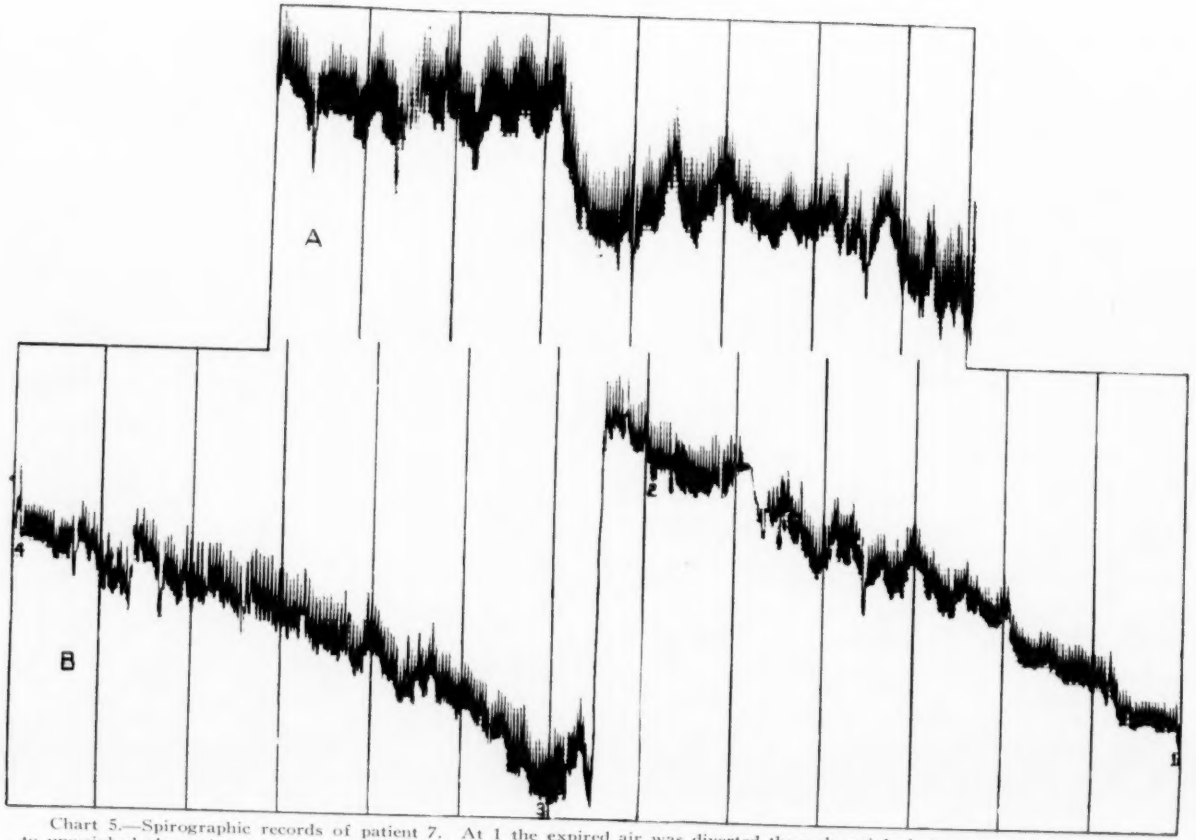

Chart 5.—Spirographic records of patient 7. At 1 the expired air was diverted through weighed absorptive containers; at 2, to unweighed absorptive containers, and at 3, to weighed absorptive containers. The test ended at 4.

spirometer, the result would be too low. If the increase occurs before the test and is maintained, the results will be unaltered. If the expiratory position increases during the test, the results will be too high.

In table 2 are tabulated the diagnoses, the relations of the changes in the expiratory position of the chest to the metabolic test, the respiratory quotients and the results of the determinations of the basal metabolic rate in percentages of normal.

In subject 3 the expiratory position of the chest increased when the mouthpiece was inserted but remained constantly elevated throughout the test, decreasing afterward. The ventilation was increased, as shown by the respiratory quotient and the great increase in amplitude. The graphs are shown in chart 2.

TABLE 2.—*Changes in Expiratory Position of Chest During Determination of Basal Metabolic Rate in Six Persons*

Case	Diagnosis	Effect of Mouthpiece	Effect of Nose-Clip	Change During Test	Respiratory Quotient	Change After Discontinuing Test	B.M.R., per Cent
3	Normal	Increased	No change	No change	0.90	Decreased	
7	Effort syndrome						
	Period I	Increased	Increased	No change	0.62	.....	+ 7
	Period II	.....	.....	No change	0.54	Decreased	+ 8
7	Effort syndrome						
	Period I	Increased	Increased	No change	0.62	.....	+ 4
	Period II	.....	.....	Increased	0.44	Decreased	+31
18	Diabetes (mild)						
	Period I	Increased	Increased	Increased	0.61	.....	+73
	Period II	.....	.....	No change	0.63	Decreased	+22
23	Pulmonary tuberculosis (after thyroidectomy)						
	Period I	Increased	Increased	Increased	0.37	.....	+47
	Period II	.....	.....	Decreased	1.77	Decreased	—15
24	Hyperthyroidism (?) Psychoneurosis (?)						
	Period I	Decreased	Increased	Decreased	....	.....	— 2
	Period II	.....	.....	No change	....	Decreased	+34

During the first study of subject 7, the expiratory position of the chest increased after the mouthpiece was inserted and again after the nose-clip was applied. Although the expiratory position fluctuated during both periods of the test, it was at the same level at the beginning and at the end, and the results of the metabolic tests were within normal limits. The graphs are shown in chart 3. In a subsequent study with this subject, the expiratory position was constantly elevated throughout the first period, but decreased between the first and second periods and increased during the second period. The increase of the expiratory position of the chest increased the calculated metabolic rate for this period 27 per cent (table 2).

In subject 18, the expiratory position of the chest increased during the first period, and remained almost constant throughout the second period. This alteration increased the apparent basal metabolism 51 per cent (table 2).

Chart 5.—Spirographic records of patient 7. At 1 the expired air was diverted through weighed absorptive containers; at 2, to unweighed absorptive containers, and at 3, to weighed absorptive containers. The test ended at 4

In subject 23, the expiratory position of the chest increased during the first period and decreased during the second period. The difference in the calculated results of the two periods was 62 per cent. If one calculated the results on the basis of a twelve-minute test period instead of two six-minute periods, the basal metabolic rate would become +16 per cent. According to the plethysmographic record, 250 cc. of oxygen was stored in the lungs at the end of the test period. If the quantity of oxygen removed from the spirometer were reduced by this amount, the basal metabolic rate would be +6.9 per cent and the respiratory quotient for the twelve-minute period, 0.85. The graphs are shown in chart 4.

In subject 24 (table 2), the expiratory position of the chest increased when the nose-clip was applied, decreased during the first period and was not materially altered during the second period. The difference between the results of the two periods is 36 per cent. The graphs are shown in chart 6.

Variations in the excretion of carbon dioxide when the closed circuit method is employed have been noted by Carpenter and several other investigators. The increased excretion has been attributed to an increased ventilation of the lungs, as illustrated by subject 3, but no good explanation has been given for the occasional decreased excretion.

During both studies of subject 7 and during the first period of study of subject 23, the respiratory quotients were low. This apparent decrease in the excretion of carbon dioxide may be attributed to the increased volume of the lungs without a proportionate increase in the rate or in the amplitude of breathing. Such circumstances allow carbon dioxide to accumulate in the lungs, as was shown in subject 23. Alterations in the expiratory position of the chest, however, do not explain the decreased carbon dioxide excretion in all subjects, as shown by subject 18, in whom the ventilation of the lungs increased. Furthermore, low respiratory quotients have been observed when the expiratory position was unaltered.

It is commonly believed by physicians and by laboratory workers that all errors in studies of metabolism by the closed circuit method tend to increase rather than decrease the apparent basal metabolism. But if the expiratory position of the chest decreases during the test, the results will be too low, as illustrated by subjects 23 and 24. It must be said, however, that any physician who is familiar with the problems encountered in the determination of the basal metabolic rate would be very doubtful of the results calculated from the graphs cited, with the possible exception of that for the second period of study of subject 23. There is no doubt that numerous reported results have been calculated from similar graphs, and these changes in the volume of the chest may account

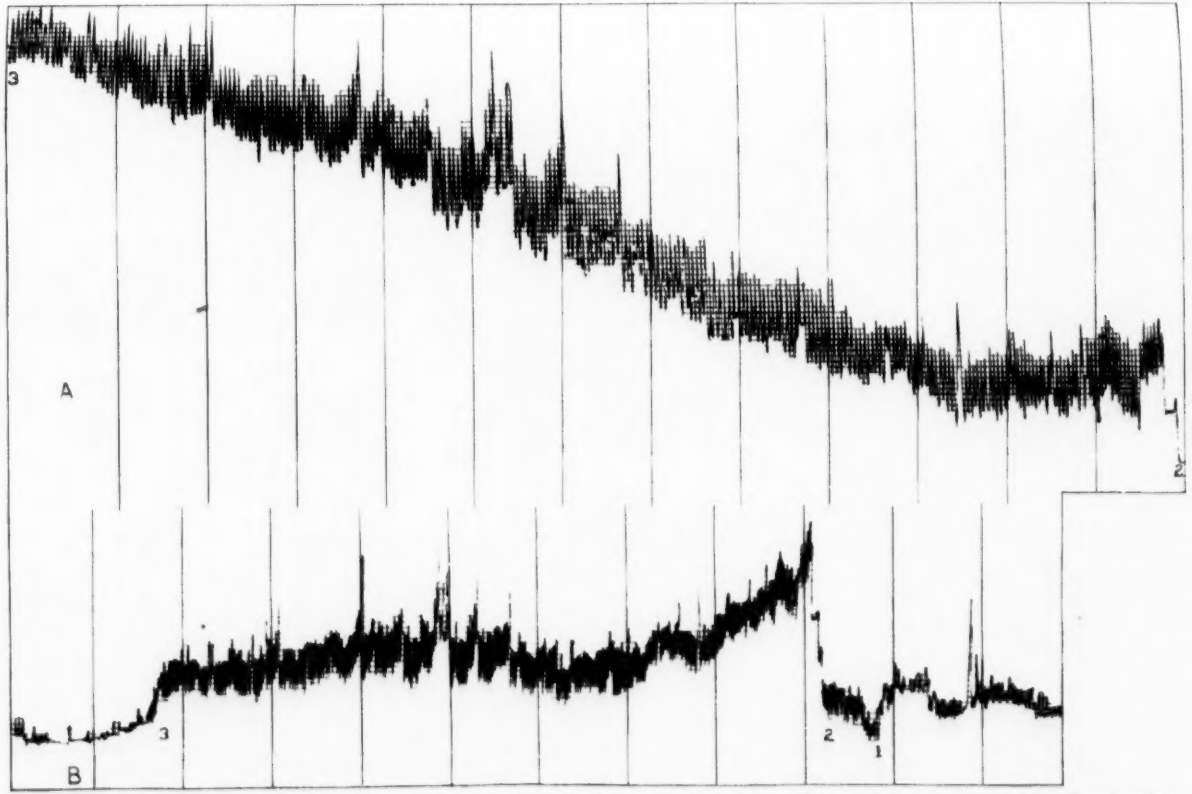

Chart 6.—At 1 the mouthpiece was inserted; at 2 the nose-clip was applied, and at 3 the metabolic test was discontinued. The carbon dioxide excreted was not determined.

for some of the fluctuating, elevated basal metabolic rates which are not in accord with the clinical findings.

The closed circuit method is the most practical clinical method for the determination of the basal metabolic rate. If test periods of from ten to twelve minutes are used, as was advocated by Benedict,[3] and Carpenter,[2] the alterations in the results attributable to changes in the expiratory position of the chest will be considerably decreased, as illustrated in subject 23.

SUMMARY

1. The influence of the determination of the basal metabolic rate on the respiratory movements has been studied in three normal and twenty diseased subjects.

2. The respiratory movements may be altered in rate, rhythm, amplitude or expiratory position of the chest, or in several combinations of these.

3. The respiratory movements were altered in every subject during the determination of the basal metabolic rate, and the ventilation was increased in twenty subjects, unchanged in one and questionably altered in two.

4. The manner in which the respiratory movements are altered varies with different subjects and may vary with the same subject during different examinations.

5. Changes in the expiratory position of the chest may alter the basal metabolic rate as determined by the closed circuit method.

6. The decreased excretion of carbon dioxide by some subjects in the basal state may be due in part to changes of the expiratory position of the chest.

7. Alterations of the expiratory position of the chest may explain some of the variances between the determinations of the basal metabolic rate and the clinical findings.

8. The alterations in the determinations of the basal metabolic rate due to changes of the expiratory position of the chest would be materially decreased if longer test periods were used.

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3. Benedict, F. G.: An Apparatus for Studying the Respiratory Exchange, Am. J. Physiol. **24**:345 (June) 1909; A Portable Respiration Apparatus for Clinical Use, Boston M. & S. J. **179**:667 (May 16) 1918.

BENIGN AND MALIGNANT NEUTROPENIA

PRESENT STATUS OF KNOWLEDGE OF THIS CONDITION, WITH REPORT OF FOUR CASES

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Even now, thirty-two years after the first recorded observations on neutropenia, there is considerable confusion, some investigators refusing to admit its existence as a true disease entity. There is ample reason for this. On reading over the published case reports, it soon becomes evident that they deal with a group of diseases and not with a single disease. The group now includes any condition showing leukopenia and neutropenia, no matter what the cause or the clinical picture.

The clinical features, including symptomatology, physical observations, pathology and treatment, are abundantly described in the literature, but one must read many publications before all phases of the disease can be fully covered or the information sought obtained. Important textbooks and systems of medicine contain only a brief discussion of the condition. This paper, arranged in more or less textbook fashion, represents a review of the established observations.

DEFINITION

Neutropenia is a grave disease of unknown etiology characterized by a marked reduction in the total number of white cells and a great reduction in the percentage of granulocytes, accompanied by aplastic, normal or hyperplastic myeloid tissue. Following the peripheral neutropenia there may be any number of lesions and symptoms which might follow the removal from the body of such an important defense mechanism. The disease may be acute or chronic.

NOMENCLATURE

Werner Schultz, in 1922, proposed the name agranulocytosis. The supply of hematologic terms is so abundant that there is little excuse for choosing such an ambiguous one. This term came into the nomenclature, no doubt, on account of its brevity. It is incorrect. The name agranulocyte was originally chosen for "neutrophils without granulations" seen in blood smears from cases of leukemia. By "agranulocytosis" is meant an increase in these atypical neutrophils, which is not

intended. Friedemann [1] being impressed by the usual severe localization of the process in the throat, suggested the name "angina agranulocytica." This name is unfortunate also, because of its intrinsic ambiguity, and because it implies that one is dealing with an infection of the mouth which causes neutropenia instead of with a syndrome of utterly unknown etiology. It is now known, also, that cases do occur without angina. Because of these confusing terms, many others have been suggested, such as mucositis necroticans agranulocytica, sepsis with granulocytopenia, monocytic angina, granulocytopenia and agranulosis. Baldridge and Needles proposed the term "idiopathic neutropenia," which seems to be a most descriptive and appropriate name. Schilling [2] suggested the name "malignant neutropenia." Rosenthal,[3] in his classification made according to the clinical manifestations and course, divided neutropenia into malignant (fatal) and benign (recovered) cases. It might be well further to divide these into two main classes as follows: (1) primary benign and primary malignant neutropenia, the true cases of benign and malignant neutropenia, in which the etiology is unknown; (2) secondary benign and secondary malignant neutropenia, the cases in which the etiologic agents are evident or in which one is dealing with examples of well recognized clinical entities.

HISTORY

If malignant neutropenia had existed to any great extent prior to 1922, it undoubtedly would have been described long before, since the disease runs such a dramatic course and usually terminates fatally. Blood counts have been made as a routine procedure in most large hospitals for the past fifty years. Pepper,[4] in his history of malignant neutropenia, stated that standard laryngologic works of fifty years ago apparently described this disease under the heading "putrid sore throat" and "gangrenous angina," and he said that Mackenzie, in his manual of diseases of the throat and nose, credited Gubler, in 1857, and Trousseau, in 1865, with having clearly distinguished the disease from diphtheria. In 1902, Brown [5] reported a fatal case of acute primary infectious pharyngitis with extreme leukopenia. This probably was the first case reported in this country. Türk [6] reported one case in 1907.

1. Friedemann, U.: Med. Klin. **19**:1357, 1923.
2. Schilling, V.: The Blood Picture and Its Clinical Significance, translated by R. B. H. Gradwohl, eds. 7 and 8, St. Louis, C. V. Mosby Company, 1929.
3. Rosenthal, N.: Am. J. Clin. Path. **1**:7 (Jan.) 1931.
4. Pepper, O. H. P.: The History of Agranulocytic Angina, J. A. M. A. **97**:1100 (Oct. 10) 1931.
5. Brown, P. K.: Am. Med. **3**:649 (April) 1902.
6. Türk, W.: Wien. klin. Wchnschr. **20**:157, 1907.

Leale,[7] in 1910, reported a case in a male child 2½ months old under the title, "Recurrent Furunculosis in an Infant Showing an Unusual Blood Picture." Baldridge and Needles [8] reported a case that occurred in 1910, pointing out that in former years it either was overlooked because the blood was not examined, or was interpreted as a symptom of exhaustion of the bone marrow, aleukemic leukemia or aplastic anemia. In 1922, Schultz [9] reported four cases, describing the clinical syndrome to which he applied the term "agranulocytosis," and he stated the belief that it was a distinct clinical entity. From that date interest in this symptom complex has continually increased. In 1923, Friedemann [3] published an article pointing out the frequent occurrence of angina in these cases. The case reported by Lovett [10] in 1924 stimulated interest in this disease in this country, and since that date many cases have been reported and many theories as to the pathogenesis and treatment suggested.

PHYSIOLOGY

Much of the accuracy in interpretation of the blood picture in this disease is dependent on an understanding of the underlying mechanism of hematopoiesis. It is with this in mind that I offer a review of the physiology of granulopoiesis, since it is with this portion of the hematopoietic tissue that one is concerned in this disease. On the basis of this knowledge of the physiology of granulopoiesis, a theory of pathogenesis may be formulated.

Location of Granulopoietic Tissue.—The granulopoietic tissue in the adult is located in the red marrow which is to be found in the ribs, the vertebrae, the sternum, the bones of the skull and the os innominatum. It is in the red marrow that granulopoiesis takes place normally.

Size of the Granulopoietic Organ.—The subject of bone marrow as a hematopoietic organ means the consideration of the entire marrow as a unit. It is an organ of no inconsiderable size, having been shown by Wetzel [11] to have a volume, in the adult human being, of 1,419 cc., which is thirteen times that of the spleen and almost equal to that of the liver. This whole structure will be found in a relatively uniform state under normal conditions. This means that the proportion of erythropoietic to granulopoietic tissue, as well as the proportions of the different levels of maturation within the two groups, is relatively con-

7. Leale, M.: Recurrent Furunculosis in an Infant Showing an Unusual Blood Picture, J. A. M. A. **54**:1854 (June 4) 1910.
8. Baldridge, C. W., and Needles, R. J.: Am. J. M. Sc. **181**:533, 1931.
9. Schultz, W.: Deutsche med. Wchnschr. **48**:1495, 1922.
10. Lovett, B. R.: Agranulocytic Angina, J. A. M. A. **83**:1498 (Nov. 8) 1924.
11. Wetzel, G.: Verhandl. d. Anat. Gesellsch., Jena, 1920, p. 82.

stant. According to studies by Doan and Zerfas,[12] in three accident cases the ratio of erythropoiesis to granulopoiesis was 1:20, 1:16 and 1:5.5. Other authors have given a ratio of 1.3. It can thus be roughly estimated that from three to twenty times more tissue is devoted to the production of granulocytes than to the production of erythrocytes, or, in other words, the volume of the granulopoietic tissue is from nine and one-half to twelve times that of the spleen. In contrasting this with the great excess of erythroid over myeloid cells in the blood stream, the reverse in the ratio must be correlated with the greater length of survival of the erythrocytes in the blood stream. It would seem from this that the granulopoietic organ is manufacturing an extremely fragile and delicate product.

Circulation of the Bone Marrow.—This is accomplished by the main nutrient artery and its accompanying veins, passing toward either epiphysis, and its capillary branches to the venous sinusoids, together with numerous anastomoses of this system with the small vessels of the bone along the shaft and with larger epiphyseal vessels in the mature bone. The capillaries that lead directly from the nutrient arteries of the third and fourth order, the "transition capillaries" of Doan, are not the functioning capillaries, as in other organs, but rather they lead into tufts of sinusoids. These sinusoids constitute the functioning vascular bed of the marrow; they have walls like capillaries and appear like them when collapsed, but when open they have the diameter and lumen of large veins. The nature of these vessels was analyzed by Minot[13] in 1900, who introduced the term "sinusoid." When the sinusoids are dilated, there is a sluggish flow of blood, which brings the maturation factors to the right concentration for the white cells. Along the border of the marrow there is a narrow zone where the blood vessels of the marrow anastomose with those of the shaft of the bone. As granulopoiesis begins, every vessel of this narrow border is patent to the circulation; that is to say, there are no collapsed intersinusoidal capillaries. No other area of the marrow has so constantly a maximum supply of blood.

Where Granulocytes Arise.—The granulocytes arise outside of the blood vessels and pass into them by their own motility. They develop around the patent, dilated sinuses or vessels of the hematopoietic tissue in the peripheral, vascular zone, and move toward their borders as they become more mature. The young granulocytes exist here in groups at the same stage of maturation and fill the sinuses. They are seen to move en masse against the walls of the capillaries until the wall is bent

12. Doan, C. A., and Zerfas, L. G.: J. Exper. Med. **46**:511, 1927.
13. Minot, G. R.: Proc. Boston Soc. Nat. Hist. **29**:185, 1901.

inward. When the stretching reaches a certain point, a leukocyte close to the wall flows in between two endothelial cells and the rest follow in rapid succession.

For this brief outline it is deemed impracticable to attempt a description of each cell. For a complete study of the bone marrow, see Sabin's article,[14] from which this information has been derived. By following the accompanying diagram, I hope the brief text will be intelligible and a clear knowledge obtained.

Maturation of Granulocytes.—The cell from which granulocytes develop (parent cell) is a subject on which there is a difference of

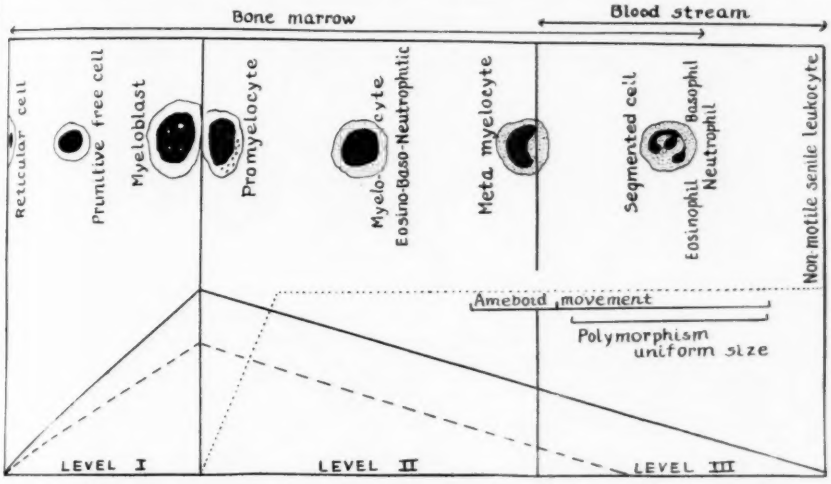

Diagram of the maturation of granulocytes, the cells being divided into three levels. The continuous curve indicates mitochondria; the dash curve, basophilia in the cytoplasm; the dot curve, granulations.

opinion. According to Sabin, this primitive cell is a reticular cell found in the interstices between the fat cells of the marrow.

Level I: This cell, with repeated divisions, gives rise to a primitive free cell. As the basophilia of the cytoplasm and the numbers of the mitochondria of this free cell reach a maximum, the cell becomes a myeloblast. This is a period of growth and division, and the primitive free cell of small size is found in the largest numbers. By the processes of basophilia and mitochondria the myeloblasts develop into promyelocytes and that is level II.

Level II: With the changing chemistry of the granules of the cytoplasm of the promyelocytes, eosinophilic, basophilic and neutrophilic

14. Sabin, F. R.: Physiol. Rev. **8**:191, 1928.

myelocytes develop. This changing chemistry of the granules continues to the senile leukocyte stage, shown by the dotted line in the diagram. In level II, granulation increases as mitochondria and basophilia in the cytoplasm decrease. Cell division ceases in level II. Basophilia may be carried over into the cells of the circulating blood, especially in rapidly developing leukocytosis. This is shown by the broken line in the diagram. Sabin distinguished three stages in the development of the myelocytes according to their granulations, and designated them A, B and C; A is the youngest myelocyte and C the oldest myelocyte ready to develop into the metamyelocyte. When the myelocytes are fully formed, there is the onset of ameboid movements, and these cells are termed metamyelocytes (juvenile form of Schilling). Ameboid movement may begin a little before the metamyelocyte stage or almost at the end of it. The metamyelocytes may appear in the blood stream, 1 per cent being considered by Schilling as normal. Hence, the line indicating the end of level II and the beginning of level III is drawn through the metamyelocyte.

Level III: From the metamyelocytes are formed cells of approximately uniform size and content of specific granulations, and ameboid activity is at its height. These are the basophils, eosinophils and neutrophils ready to be delivered to the blood stream. In level III, the cells show functional maturity with a uniformity in size. Division no longer takes place, having ceased in level II, and polymorphism occurs. The leukocytes, according to Arneth, become more mature in the circulating blood, involving nuclear changes, and finally pass into the nonmotile phase; the cells in this stage are the fragile forms with easily ruptured membranes seen in fixed films.

Rhythmic Delivery of Granulocytes.—The rhythmic delivery of granulocytes from the marrow to the blood stream has been demonstrated by Sabin and her co-workers.[15] Shaw [16] demonstrated that the afternoon rise is but a part of a diurnal rhythm, with a second rise about midnight. This rhythmic delivery of cells persists in cases with leukopenia and leukocytosis, being particularly striking in the latter. The approximate hourly delivery of cells to the blood stream suggests that the time for the maturation from metamyelocyte to granulocyte might be expressed in units of hours or minutes, while the time for the maturation from promyelocyte through to metamyelocyte may possibly be expressed in units of days, probably from three to seven. With the concept in mind that bone marrow, as a hematopoietic organ, is the place where granulocytes are made, that it holds a large store almost ready

15. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: Bull. Johns Hopkins Hosp. **37**:14 (July) 1925.

16. Shaw, A. F. B.: J. Path. & Bact. **30**:1, 1927.

for delivery and that its store of immature forms is small in numbers but with exceedingly high potentiality toward multiplication, growth and maturation, the question of the mechanism to maintain such a normal structure becomes a major problem of hematology. Two different processes must be analyzed: first, the mechanism of the delivery of cells to the circulation, and second, the mechanism of maturation.

Mechanism of Delivery.—The question of how great a part vasomotor influences play in the mechanism of delivery is uncertain. Experiments concerning the response of the marrow to nerve stimuli have not been sufficiently controlled with reference to the normal rhythm of delivery to allow the forming of any definite conclusions.

There is more definite information available concerning chemotactic factors. It is possible to call the cells from the marrow by administering inactivated typhoid bacilli, depleting the bone marrow of myelocytes and leaving only promyelocytes and myeloblasts. This experiment was performed by Doan and his associates,[17] and can be expressed as representing a condition due to a chemotactic factor minus a maturation element. The cells of the marrow showed no toxic effect, and the marrow readily regenerated after the experiment. Of the many substances that have been shown to call leukocytes from the bone marrow, nucleic acid is most likely to be a part of the normal mechanism. An excellent contribution on this subject is that of Doan and others,[18] in a study of the effect of large doses of nucleic acid. Their study of the bone marrow showed clearly the chemotactic effect of the nucleic acid, with the massing of leukocytes around the patent sinusoids, a marked diapedesis into the vessels and the vacant areas of the marrow from which the granulocytes had been drawn. They also found that the granulocytes could be called from the marrow by the split products of nucleic acid, the purine bases, adenine and guanine. It is thus likely that nucleic acid and its derivatives are important physiologic factors in the chemotactic reaction, and that the showers of nonmotile leukocytes in the circulating blood may give a rhythmic discharge of such products (nucleic acid, adenine, guanine, etc.) into the circulation. In later experiments on nucleic acid and its degradation products, Doan [19] gave the following conclusions:

1. Nucleic acid and its degradation products exert a chemotactic effect on normal myeloid foci with a prompt effective increase in the delivery of granular leukocytes to the peripheral circulation under a controlled physiologic or rhythmic

17. Doan, C. A.; Cunningham, R. S., and Sabin, F. R.: Contrib. Embryol. **16**:163, 1925.

18. Doan, C. A.; Zerfas, L. G.; Warren, S., and Ames, O.: J. Exper. Med. **47**:403 (March) 1928.

19. Doan, C. A.: The Neutropenic State, J. A. M. A. **99**:194 (July 16) 1932.

mechanism. 2. Repeated large intravenous injections tend neither to exhaust nor to cause a malignant hyperplasia of the myeloid elements in normal animals. 3. A short course of injections stimulates a myeloid hyperplasia of normal marrow without otherwise injurious consequences, which is reflected by a relative and absolute increase in the amphophilic granulocytes in the blood stream of rabbits.

Of maturation factors there is but meager knowledge, but those bacteria that produce a sustained leukocytosis introduce such a factor as they produce an increased division, growth and maturing of the less mature leukocytes in the marrow far beyond the normal amount. Bacon and his co-workers [20] considered that even in infections the stimulus to an increased activity of the marrow comes from altered body proteins. The relationship of the degree of leukocytosis to the resistance of the animal in infections has been repeatedly confirmed since Metchnikoff, and thus, as long as none of the substances involved in these reactions is known, variations in the response of the animal must be studied in terms of the amount of the infection and possibly differences in the power of the hematopoietic tissues to respond. One might venture to speculate, though, that the resistance of the patient may not depend on the power of the granulopoietic tissue to respond, but on the power of the tissues producing the maturation factor to respond. The only definite knowledge of maturation factors concerns erythrocytes. The recent application of the liver diet to patients with pernicious anemia and the isolation from liver of the specific substance by Cohn and his associates [21] involve the discovery of a maturation factor. Minot and Murphy [22] have shown that by the liver diet the normal mechanism is restored by the speedy appearance in the peripheral blood of reticulated erythrocytes of normal size. Liver extract does not supply a maturation factor for granulocytes. No doubt there is a similar maturation factor in the body to regulate the normal production of granulocytes. The modern aspect of this problem involves an investigation of the chemical maturation factors which determine the granulocytes. These chemical factors are to be sought in certain organ extracts, as well as in specific dietary factors some of which may be vitamins.[23]

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20. Bacon, D. K.; Novy, F. O., and Eppler, H. H.: Factors in Leukocytosis, Arch. Int. Med. **30**:229 (Aug.) 1922.

21. Cohn, E. J.; Minot, G. R.; Fulton, J. F.; Ulrichs, H. F.; Sargent, F. C.; Weare, J. H., and Murphy, W. P.: J. Biol. Chem. **74**:69, 1927.

22. Minot, G. R., and Murphy, W. P.: Boston M. & S. J. **195**:410, 1926; Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

23. Whipple, G. H.: Robscheit-Robbins, F. S., and Hooper, C. W.: Am. J. Physiol. **53**:236, 1920. Robscheit-Robbins, F. S., and Whipple, G. H.: ibid. **72**: 408 and 431, 1925. Drew, A. H., and Mottram, J. C.: Lancet **2**:1202, 1921. Koessler, K. K., and Maurer, S.: Treatment of Pernicious Anemia with a High Caloric Diet, Rich in Vitamins, J. A. M. A. **89**:768 (Sept. 3) 1927. Cohn, Minot, Fulton, Ulrichs, Sargent, Weare and Murphy.[21] Minot and Murphy.[22]

Function of Neutrophils.—Roberts and Kracke [24] said: "We have evidence that the mere loss of granulocytes for seven days is incompatible with life." Their absence gives new slants and intimations on the part they play in immunity. Granulocytes are one of the chief sources of immunity. With their disintegration and released ferments they give much active daily immunity to the body. They are thought to be the source of complement, and complement is present in the plasma, owing probably to the continued disintegration of neutrophils. Complement is probably the most important single factor in the destruction of bacteria and the defense of the tissues. There is some evidence to show that granulocytes may be the chief source of supply for many of the various types of immune bodies, such as bacteriolysins, hemolysins and precipitins. The rôle of neutrophils in infections is well known.

Normal Destruction of Neutrophils.—Weiskotten,[25] experimenting with rabbits, showed that the life span of the neutrophil in the blood stream was about four days. The case studies by Roberts and Kracke [24] seem to prove that the life span of the human neutrophil is about the same. Some idea can thus be had as to the enormous numbers of granulocytes to be consumed daily, termed physiologic degeneration. Cells in the nonmotile phase appear in the blood stream in showers, indicating that there is death of many granulocytes in the blood stream. There are various physiologic outflowings of granulocytes from the blood into the tissues, with consumption in the tissues. There is elimination of neutrophils into the saliva and probably into the entire digestive tract and onto all mucous membranes. There is apparently a gradual loss of granulopoietic tissue with advancing years. Custer and Ahlfeldt [26] studied the tibia, the femur, rib, sternum and vertebra in a hundred unselected cases and found that the cellularity of these marrows decreased with advancing years of life, the decrease corresponding in rapidity to the order named. The response of these marrows to a hematopoietic stimulus of a given intensity is in the following order: vertebra, sternum, femur, rib and tibia.

THEORIES OF PATHOGENESIS

Explanation of the pathogenesis of this disease rests on hypothesis alone. In reviewing the literature one finds many explanations. I shall attempt to group these hypotheses so that they may be covered as briefly as possible.

24. Roberts, S. R., and Kracke, R. R.: Agranulocytosis, J. A. M. A. **95**:780 (Sept. 13) 1930.

25. Weiskotten, H. G.: Am. J. Path. **6**:183, 1930.

26. Custer, R. P., and Ahlfeldt, F. E.: J. Lab. & Clin. Med. **17**:960 (July) 1932.

Predisposing Causes.—Neutropenia is seen most frequently in women. Hueper [27] found a ratio of three and one-half women to one man, or 77.5 per cent in women. In the final analysis, it may be found that neutropenia and leukopenia, chronic and acute, do not predominate in either sex. Roberts and Kracke [28] presented a table compiled from eight thousand leukocyte and differential counts which shows this trend in chronic cases, only 56 per cent being in female patients. Practically all of the typical cases of primary benign and malignant neutropenia have occurred in the fourth decade of life—from 41 to 58 years of age. Cases have occurred in children, in young adults and past the age of 60, but they are more rare. Under predisposing causes must also be mentioned the coincidence of previous disease of the liver and the gallbladder with malignant neutropenia, which has been stressed by Hueper and Garrison [29] and other authors.[30] The majority of the cases of benign and malignant neutropenia reported have occurred in Germany and the United States. Other predisposing causes may be those drugs and chemicals containing the benzene ring, the arsenicals, mesothorium, trinitrotoluene, x-rays and the gamma rays of radium. Certain infections may also be predisposing cases. Cases coming under this heading are classed as secondary benign and secondary malignant neutropenia.

Organisms as a Cause.—Many authors [31] think that malignant neutropenia is an infectious disease, but attempts to reproduce malignant neutropenia by injecting into animals organisms isolated from lesions, from the bone marrow and from the blood stream of patients have failed to give conclusive information. A review of the literature discloses a large number of patients giving the history of Vincent's angina, trench mouth or the extraction of teeth prior to the clinical onset. Seiferth [32] reported a case of malignant neutropenia following tonsillectomy. These infections might be interpreted as a result and not a cause, as the

27. Hueper, W. C.: Agranulocytosis (Schultz) and the Agranulocytic Symptom Complex, Arch. Int. Med. **42**:893 (Dec.) 1928.

28. Roberts, S. R., and Kracke, R. R.: Ann. Int. Med. **5**:40 (July) 1931.

29. Hueper, W. C., and Garrison, L. E.: S. Clin. North America **10**:407 (April) 1930.

30. (*a*) Schaefer, R.: Deutsches Arch. f. klin. Med. **151**:191 (May) 1926. (*b*) Aubertin, C., and Lévy, R.: Arch. d. mal. du cœur **21**:369, 1928. (*c*) Peritz, E.: Zentralbl. f. Chir. **54**:2129 (Aug. 20) 1927. (*d*) Hueper, W. C., and O'Conner: Laryngoscope **38**:679, 1928.

31. Feer, W.: Agranulocytosis, Schweiz. med. Wchnschr. **56**:551, 1926; abstr., J. A. M. A. **87**:366 (July 31) 1926. Weiss, J.: Wien. Arch. f. inn. Med. **14**:303 (May) 1927. Zadek, I.: The Agranulocytosis Question, Med. Klin. **21**:688 (May 8) 1925; abstr., J. A. M. A. **85**:77 (July 4) 1925. David, W.: Med. Klin. **21**:1229 (Aug. 14) 1925.

32. Seiferth, L. B.: Deutsche med. Wchnschr. **57**:1930 (Nov. 13) 1931.

patients may have been suffering from an unrecognized chronic granulopenia. The depression in the bone marrow in this disease may be caused by a hidden or a latent infection that has been present for a long time, the depressed marrow then being unable to cope with an emergency. Fried and Dameshek,[33] in their experimental work of producing neutropenia, infected rabbits with Salmonella suipestifer by way of the blood stream. By injecting small doses or overwhelming doses they could produce two types: (1) cases in which the animals recovered and (2) fulminating cases ending fatally. The blood picture showed leukopenia and neutropenia. In the cases in which recovery occurred the bone marrow showed areas of necrosis with patches of proliferation. In the fulminating cases there was but little evidence of myeloid proliferation. Piersol and Steinfield[34] found that a long-continued granulopenia could not be induced in healthy rabbits by the use of a small group of common bacteria. Marked leukopenia and neutropenia due to an infection (secondary neutropenia) should be distinguished from typical or primary neutropenia, in which the primary lesion is in the blood or the bone marrow or in both and infection follows the peripheral neutropenia. Therefore, the opinion that the organisms isolated in this disease are the cause does not seem to be well substantiated. It seems more likely that the organisms are secondary invaders growing profusely in a system devoid of granulocytes. It is not a new experiment to exhaust the bone marrow, one or all of its component parts, experimentally with various organisms, so that producing leukopenia and neutropenia experimentally with these agents is attacking the problem, at least from an etiologic standpoint, from the wrong angle.

Septic and Toxic Processes.—A number of authors have stated that the blood picture in benign and malignant neutropenia is due to a marked effect on the myeloid cells by a septic or a toxic process; others, that it is the exhaustion of normal bone marrow as the result of a nonspecific sepsis.[35] Schultz[9] said that it is a disease per se, being caused by a specific agent that has a particular affinity for the myeloid system, but he did not state of what character the specific agent might be. Stocké[36] expressed the belief that malignant neutropenia is not a special disease, but an abnormal reaction to sepsis. Dameshek and Ingall[37]

33. Fried, B. M., and Dameshek, W.: Experimental Agranulocytosis, Arch. Int. Med. **49**:94 (Jan.) 1932.

34. Piersol, G. M., and Steinfield, E.: Granulopenia (Granulocytopenia), Arch. Int. Med. **49**:578 (April) 1932.

35. Ehrmann, R., and Preuss, J.: Klin. Wchnschr. **4**:267 (Feb. 5) 1925.

36. Stocké, A.: Folia haemat. **40**:40, 1930.

37. Dameshek, W., and Ingall, M.: Am. J. M. Sc. **181**:502, 1931.

also shared this view. Zikowsky [38] expressed the belief that malignant neutropenia is a severe form of sepsis occurring in a weakened organism, resulting in injury to the granulopoietic tissue and paralysis of the organ complex (liver, spleen and endocrine glands), the secretions of which stimulate the bone marrow and regulate the entrance of the granular cells into the blood stream. He therefore believes that sepsis is the primary cause. Zadek [39] expressed the opinion that a virus of sufficient potency to destroy the granulopoietic tissue so completely could not uniformly spare all of the closely related contiguous cells. There are a number of observations which tend to eliminate the hypothesis of a septic or a toxic process acting on the myeloid tissue. The neutropenia may precede the appearance of local signs of infection,[28] or there may not be any demonstrable infection.[40] Also, the neutropenia may be definitely periodic, as in the case reported by Rutledge and his co-workers,[41] and in case 3 of Doan's series.[19] Biopsies [3] and postmortem studies [42] of the marrow often show a peripheral neutropenia and leukopenia with myeloid hyperplasia.

Hyperergic Inflammation.—A few authors believe that benign and malignant neutropenia may be a form of hyperergic inflammation (allergy) in which the bone marrow is the point of least resistance. Schilling [2] has produced a blood picture similar to malignant neutropenia experimentally in anaphylaxis, so that he thinks it may be an anaphylactic condition instead of an individual disease. Bromberg and Murphy [43] reported a case following prophylactic vaccination against typhoid. Kracke [44] reported a case. He said: "The question of typhoid prophylaxis as a whole or partial cause of the condition must be considered." It is known that inactivated typhoid bacilli have a marked chemotactic effect on the bone marrow. Meyer [45] reported a case following malarial therapy. A few of the cases showing eosinophilia during the attack suggest anaphylaxis. These cases may have resulted from an overwhelming reaction to foreign protein in a sensitive subject.

38. Zikowsky, J.: Wien. klin. Wchnschr. **44**:203 (Feb. 6) 1931; 226 (Feb. 13); 259 (Feb. 20) 1931.

39. Zadek, I.: Med. Klin. **21**:694 (May 8) 1925.

40. (*a*) Author's case 4. (*b*) Hamburger, L. P.: Bull. Johns Hopkins Hosp. **48**:339, 1931.

41. Rutledge, B. H.; Hansen-Prüss, O. C., and Thayer, W. S.: Bull. Johns Hopkins Hosp. **46**:369 (June) 1930.

42. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Am. J. M. Sc. **183**:104 (Jan.) 1932.

43. Bromberg, L., and Murphy, P.: Agranulocytic Angina Following Prophylactic Typhoid Vaccination, J. A. M. A. **92**:1266 (April 13) 1929.

44. Kracke, R. R.: Am. J. Clin. Path. **1**:385 (Sept.) 1931.

45. Meyer, A.: Deutsche med. Wchnschr. **57**:226 (Feb. 6) 1931.

Congenital and Familial Anomaly.—A familial tendency to diseases of the hematopoietic tissues of one type or another is a possibility. Hart [46] suggested a familial tendency, having observed malignant neutropenia in two sisters. Wolff [47] reported malignant neutropenia and myeloblastic leukemia as reactions to the same infection in a brother and sister. Bickel [48] said that congenital hematopoietic insufficiency is a possible explanation. Congenital granulopoietic insufficiency seems to have been proved in some cases, but the granulopoietic tissue in most of these patients had, so far as is known, functioned normally for many years. The cyclic and recurring nature of many cases is hard to explain on the basis of a congenital lesion. Blumer [49] dismissed the possibility of a congenital anomaly with the following statement: "The same patient has reacted with the usual leukocytosis and granulocytosis to one attack of an infection and has shown a neutropenic and leukopenic reaction to another attack." Whether certain patients have a constitutional and abnormal functionally limited bone marrow for making blood is as yet a theoretical question.

Chemical Poisoning.—Chemical poisoning of the granulocytic apparatus is possible, but usually drugs do not have an affinity for just the granulopoietic tissue. Farley [50] reviewed from the literature thirty-nine cases in which the function of the bone marrow was depressed following the use of various preparations of arsphenamine. The symptoms varied from those of purpura hemorrhagica to those of severe aplastic anemia and malignant neutropenia, depending on whether the principal effect was on the granulopoietic, megakaryopoietic or erythropoietic tissues, or on all of these combined. Since it is known that benzene is a powerful leukocytic depressant and taking into consideration the thirty-nine cases following the use of arsphenamine, it might be possible that any drug containing the benzene ring could be an etiologic factor, such as the many coal tar derivatives on the market which are used by the public indiscriminately. These drugs may serve to weaken the hematopoietic tissue. Benzene usually does not produce typical benign and malignant neutropenia, but a depression of all the bone marrow elements, so that anemia, purpura and sometimes methemoglobinemia, as well as leukopenia and neutropenia, are produced. Kracke [51] expressed the belief that benzene probably can be administered in such dosage as to produce marked granulopenia with no apparent effects on

46. Hart, V. K.: Laryngoscope **37**:357 and 798, 1927.
47. Wolff, E.: Folia haemat. **44**:38 (April) 1931.
48. Bickel, L.: Wien. klin. Wchnschr. **42**:1186 (Sept. 12) 1929.
49. Blumer, G.: Am. J. M. Sc. **179**:11 (Jan.) 1930.
50. Farley, D. L.: Am. J. M. Sc. **179**:214 (Feb.) 1930.
51. Kracke, R. R.: Am. J. Clin. Path. **2**:11 (Jan.) 1932.

either erythrocytes or platelets. He has performed experiments on rabbits which bear out this point. In 1910, Selling [52] reported observations on three girls who had been working in a rubber factory and were suffering from benzene poisoning, characterized by "agranulocytosis" and complicated by purpura and hemorrhages. One of them had quit her work long before, illustrating the cumulative and delayed effect of the chemical on the hematopoietic tissues. This is a most important point to consider in connection with the coal tar products. Later, Selling [53] experimented with benzene as a leukotoxin. He injected benzene subcutaneously into rabbits, and demonstrated the production of leukopenia with little effect on the erythrocytes. Jacob and Douady [54] reported a case of malignant neutropenia in a patient treated with injections of gold sodium thiosulphate, showing the probable toxicity for the granulopoietic tissue of gold preparations. It has been known for some years that the granulopoietic tissues can be depressed with various chemicals, so that producing benign and malignant neutropenia experimentally with these agents is also attacking the problem, at least from an etiologic standpoint, from the wrong angle. Typical cases of primary neutropenia are not due to chemical poisoning.

Paralysis of the Bone Marrow.—Paralysis of the bone marrow, as expressed by some authors, cannot be considered at this time owing to the lack of knowledge concerning the regulation of the bone marrow by a nerve mechanism.

Endogenous Disturbance of Production of Chemotactic and Maturation Factors.—It is known that two different processes must be considered concerning the mechanism to maintain production and destruction of granulocytes at a constant level: (1) the mechanism of delivery of cells to the circulation and (2) the mechanism of maturation. It appears from reports on sternal biopsies [3] and on autopsies [42] that one or the other of these processes might be at fault independently in different cases. In typical cases of malignant neutropenia with myeloid aplasia, the part of the bone marrow that manufactures the granular leukocytes (level I, chart) has ceased to function, or nearly so. The life of the granular cells in the blood stream in normal conditions of health is considered to be from three to five days; therefore, when manufacture in level I ceases and the supply in levels II and III of the bone marrow is exhausted, the granulocytes of the blood stream would totally disappear in from three to five days after the exhaustion of levels II and

52. Selling, L.: Bull. Johns Hopkins Hosp. **21**:33, 1910.

53. Selling, L.: Bull. Johns Hopkins Hosp. **27**:83, 1916.

54. Jacob and Douady: Bull. et mém. Soc. méd. d. hôp. de Paris **54**:798 (May 19) 1930.

III. There is little evidence that the granulocytes are abnormally destroyed in the blood stream. The bulk of all evidence points to the fact that the primary lesion in these cases, so far as is known, is in the granulopoietic areas of the bone marrow, and that this condition precedes the clinical symptoms and local infections. What, then, accounts for the condition of the granulopoietic tissue? It seems reasonable to suppose that the primary lesion is not in the bone marrow but in the organ or tissue which gives rise to the substance (factor) that keeps maturation of the granulocytes regulated to a normal level or regulated so that destruction and production are kept constant. The textbook description of pernicious anemia can, with little alteration, be made to apply astonishingly well to this type of malignant neutropenia, the principal alteration being the substitution of the granulopoietic for the erythropoietic tissue. There may be remissions in both. Perhaps patients who appear to have fulminating cases of malignant neutropenia have had many attacks and remissions in the past. In each of these diseases there are lesions that one would expect following the depression of one or the other of the component parts of the marrow. It is easy to see how a great reduction of the granulocytes would be more rapidly fatal than a great reduction of erythrocytes. A maturation factor for erythrocytes has been found; it now remains to find a maturation factor for granulocytes. Chemical analysis of bacteria known to cause a sustained leukocytosis, owing to the fact that they supply both a chemotactic and a maturation factor, might lead to a solution. It seems more logical to search within the body for the specific organ extract regulating granulopoiesis. Animal experimentation, with the removal of different glands of internal secretion or the destruction of other tissues by various substances, with a careful check on the granulocytes, might lead to valuable information not only as to etiology but as to treatment.

The other group of cases showing peripheral neutropenia with slight hypoplasia, normal, moderate or marked hyperplasia of the myeloid tissue, may be considered as due to a lack of the chemotactic factor. The cells may be growing and maturing, but are not being called to the circulating blood. It is apparently in these cases that the patients recover spontaneously or are benefited by nucleotides. The normal stimulus for calling the granulocytes from the marrow to the circulating blood has been shown by experimental work[55] to be the liberated products (nucleic acid, adenine, guanine, etc.) from disintegrating granulocytes in the blood stream. This theory could account for the failures in the

55. (*a*) Doan, Zerfas, Warren and Ames.[18] (*b*) Ames, Delano, and Huntley, A. A.: The Nature of the Leucocytosis Produced by Nucleinic Acid: A Preliminary Experimental Study, J. A. M. A. **29**:472 (Sept. 4) 1897. (*c*) Jackson, Henry, Jr.: J. Biol. Chem. **59**:529 (April) 1924.

treatment of patients with nucleotides, as clinically the cases were the same as those of the patients who recovered. If the maturation factor is absent, a chemotactic factor would be of little value.

PATHOLOGY

Pathology of Lesions.—The peculiar inflammatory reaction seen in lesions accompanying benign and malignant neutropenia is merely a consequence of the absence of circulating granular leukocytes. Tissue necrosis and ulceration, whenever they occur, present only the distinguishing feature of being unaccompanied by polymorphonuclear leukocytic infiltration. The cellular reaction that does occur is comprised mainly of lymphocytic infiltration and the appearance of endothelial leukocytes or macrophage cells. There is a lack of development of the protective inflammatory barrier to infection, which is the reason for the spread of such infection. The most common site for the development of focal regions of infection and necrosis is along various parts of the gastro-intestinal tract, particularly at those points where bacteria are normally abundant. It is possible that the lesions along the gastro-intestinal tract are affected by the usual bacterial inhabitants which gained the ascendency as a result of the removal of the protective mechanism partially inherent in the normal function of the granular leukocytes.

Pathologic Changes in the Bone Marrow.—In practically all fatal cases the bone marrow is degenerated to a great extent, often liquid, and varies in color from red to straw. There may be areas of patchy necrosis in the marrow. Normoblasts and megakaryocytes are present usually in their normal numbers, but the myelocytes and polymorphonuclear cells are absent or nearly absent. There may be a few myeloblasts, some showing mitosis, but they are fewer than are present normally. In other cases, particularly with the maintenance of the gross fatty structure, granulocytes may be completely absent, or nearly so, but erythrocytes, lymphocytes and endothelial leukocytes are present. The latter two types apparently may be actually increased. The aplasia of the marrow involves the granulocytes only, and they are absent even under the oxydase reaction. In one fatal case reported by Fitz-Hugh and Krumbhaar [42] the bone marrow showed a myeloid hyperplasia. In Rosenthal's [3] benign cases of neutropenia, sternal biopsies disclosed a normal, light or marked myeloid hyperplasia. It is therefore apparent that two types of pathologic change underlie cases of neutropenia. In one type, maturation of granulocytes has ceased, and there are peripheral neutropenia and myeloid aplasia; in the other type, there is arrest of maturation with peripheral neutropenia and normal or hyperplastic myeloid tissue.

Hallermann [56] reported a case of malignant neutropenia which showed typical lymph follicles in the bone marrow. It is known that typical follicles are occasionally encountered in normal bone marrow, so that they probably did not have any connection with the disease in question.

Infection of the Bone Marrow.—Yellow marrow is at all times a potential reserve for blood formation, and there is some evidence that it may be a special factor of safety in infection. Müller,[57] in a series of cases of influenza, found that the red marrow had been invaded by organisms and damaged enough to cut down granulopoiesis, while the yellow marrow had escaped infection and was becoming active. It will be remembered that influenza is characterized by leukopenia. Müller,[58] in another article, reported the vertebral marrow involved in more than 80 per cent of a series of different infections and the marrow of the long bones in only 25 per cent. Infection of the bone marrow in benign and malignant neutropenia has never been demonstrated except in terminal septicemia. The work along this line, however, has not been exhaustive, and further research may show this to be a great factor, especially in fulminating cases. Infection could take place quickly in a marrow devoid of granulocytes, and prevent the resumption of granulopoiesis.

Pneumonia in Malignant Neutropenia.—When pneumonia occurs, it is characterized by the appearance of a diffuse edema. The gross picture is similar to that of influenzal pneumonia if death occurs during the neutropenia. Subpleural hemorrhages are frequently observed. Microscopically, there is no evidence of pneumonia, but a diffuse acute hemorrhagic edema with little phagocytosis and no signs of inflammation.

Pathologic Changes in the Spleen.—The reaction in the spleen was found to depend on the predominance of toxic or septic symptoms. In cases observed at autopsy, a splenic tumor, partly of splenic character, was disclosed in some cases. Enlargement of the spleen in some cases has been found to be due to a great increase in the reticulo-endothelial cells, which outnumber the lymphoid cells. The lymph follicles are not prominent on the cut surface. Microscopically, the sinuses are filled with erythrocytes, proliferating reticulo-endothelial cells and lymphoid cells. Oxydase-positive cells are absent or scanty. The lymph follicles are small and atrophic, and there are no young cells or lymphoblasts in the germinal centers, only mature lymphocytes. Small anemic infarcts are occasionally seen.

56. Hallermann, W.: Folia haemat. **42**:1 (Aug.) 1930.
57. Müller, E. F.: Ztschr. f. Hyg. u. Infectionskr. **93**:223, 1921.
58. Müller, E. F.: Virchows Arch. f. path. Anat. **246**:49, 1923.

Pathologic Changes in the Liver.—The liver may be somewhat enlarged and show cloudy swelling. Microscopically, some cases have shown fatty degeneration, and occasionally small multiple foci of necrosis. There is an increase in Kupffer's cells. There are bile casts in the bile capillaries and bile pigment in the hepatic cells. Sometimes there are interstitial lymphatic infiltrations.

Pathologic Changes in the Lymph Nodes.—The pathologic changes in the lymph nodes as given by Hueper and Garrison [29] are as follows: The submaxillary, cervical, peribronchial and mesenteric lymph nodes are in general enlarged, and they sometimes contain hemorrhages. Microscopic examination reveals atrophy of the lymph follicles; there are no young lymphocytes in the germinal centers, only mature lymphocytes being present. There is a proliferation of the reticulo-endothelial cells.

LABORATORY DATA

The results of laboratory examinations in this disease are of the greatest importance, since without following the total leukocyte count, as well as the differential count, at frequent intervals, an accurate diagnosis cannot be made and the progress of the disease followed. It is necessary to distinguish this syndrome from a number of other diseases characterized, in part, by low total leukocyte counts as well as by lymphocytosis. As a rule, this is not difficult and can be done easily on a basis of results of clinical and laboratory examinations. It is probable that many cases with characteristics of malignant neutropenia are overlooked because of inadequate laboratory studies. For comparable results, counts should be made in these cases at the same hours each day; thereby cognizance is taken of the rhythmic delivery of granulocytes to the blood stream. Daily leukocyte and differential counts are essential in following the results in any form of treatment. In some cases it is well to make two or three examinations in the twenty-four hour period.

Total Leukocytes.—One of the outstanding laboratory findings in this disease is, of course, the marked leukopenia. In a severe, fulminating case the total leukocytes may be so low as to be practically uncountable. It is necessary in these low counts to use a 1 : 10 dilution of the blood instead of the usual 1 : 20, and greater accuracy may be had by using the Fuchs-Rosenthal counting chamber, which gives a depth of 0.2 mm. Several square millimeters should be counted and an average taken. In the mild cases with a relatively slow course, the number of total white cells may be quite normal at first, but may gradually fall to 1,000 or less per cubic millimeter. The entire drop in the leukocyte count at the beginning of the disease is due to the disappearance of granulocytes. In fulminating cases, when first seen, the total leukocyte

count may be 700 or 600. In some cases the counts are reported as low as 200 total white cells. In practically all cases the counts are below 2,000.

Granular Leukocytes.—The second most outstanding laboratory finding in this disease is the neutropenia. The neutrophilic granulocytes may range from around 40 or 30 per cent in the most chronic and less severe cases to a total absence in the fulminating cases. One striking feature is that their morphology, in practically all cases, is normal. Complete studies on the changing differential counts of the white blood cells have been made in but relatively few of the reports recorded in the literature, chiefly, it is presumed, because of the rapid course of the disease, and secondly, because of the extreme leukopenia, which makes finding of the cells difficult. Dameshek and Ingall [37] reported in one case the gradual disappearance of granulocytes, most of which were immature forms. A terminal rise in immature granulocytes has been commented on by Krumbhaar,[59] who, observing this phenomena in fatal cases of mustard gas poisoning associated with marked leukopenia, called it a "myelocytic crisis." Schilling [2] explained its mechanism thus: The toxic or infectious agent destroys most of the granulopoietic tissue; the remaining granulocytes, however immature, gradually or suddenly appear in the blood stream, until finally the available stock of granulocytes becomes totally exhausted, the total count gradually decreasing during this time. Schilling called this a "degenerative shift." In most of the fatal cases of this disease, the maturation factor is absent, but the chemotactic factor is present, causing the granulocytes to continue being delivered to the circulation until the supply is exhausted. These are the cases showing myeloid aplasia. The amount of the chemotactic factor could determine the rate of delivery. In cases of "maturation arrest," the normal supply or an oversupply of granulocytes is in the hematopoietic tissue, but a chemotactic factor to call them to the circulation is absent. In these cases, when a chemotactic factor is supplied, mature cells are ready to be delivered to the circulation and few young forms are seen. These observations make it impossible to say at times, from the appearance of the blood slide alone, whether the patient is recovering or whether there is just an "agonal" outpouring of the remaining young cells. The total count in conjunction with the differential count aids in making the decision. The data on stab or rod forms in this disease are meager. In two of the four cases reported by Friedemann,[60] the finding of rod or stab nuclears is recorded. In one case, two days after the first roentgen treatment and four hours after

59. Krumbhaar, E. B.: J. M. Research **40**:497, 1919; Rôle of the Blood and the Bone Marrow in Certain Forms of Gas Poisoning: I. Peripheral Blood Changes and Their Significance, J. A. M. A. **72**:39 (Jan. 4) 1919.

60. Friedemann, U.: Deutsche med. Wchnschr. **53**:2193 (Dec. 23) 1927.

the second, there were 34 per cent. In the other case, they ranged from 2 to 7 per cent during recovery.

In practically all of the cases reported in the literature, the eosinophils were either absent or present in normal or slightly increased percentage. In all of the cases to be reported, they were absent during the attack. The basophils are either absent or in normal percentage.

Viability of Granulocytes.—Rutledge and his associates [41] studied the viability of the granulocytes in a case of cyclic benign neutropenia by supravital staining. They found that just before and during an attack the motility of the neutrophilic granulocytes became much reduced, and their vitality, as well as their capacity to take the neutral red dye, was much diminished. Their viability was frequently no more than half of the normally expected time of life, and their motility between attacks never approached normal. The eosinophils during this time (they were always increased during an attack in this patient) showed, on the contrary, great motility and increased viability.

Lymphocytes.—The lymphocytes may at first be present in their normal absolute numbers, the entire drop in the total leukocyte count being due to the disappearance of neutrophilic granulocytes. As the disease becomes more and more severe there is a relative increase, but in most instances an absolute decrease, of lymphocytes. They may become greatly reduced. The morphologic characteristics of all the lymphocytes are, as a rule, perfectly normal. With a total normal count of 6,000, there are in the blood stream from 21 to 25 per cent lymphocytes and from 4 to 8 per cent endothelial leukocytes; which means, combining the two, that there are from 1,500 to 1,980 nongranular white cells per cubic millimeter in the circulating blood under normal conditions. Therefore, when the total number of cells in malignant neutropenia reaches from 1,980 to 1,500 per cubic millimeter, if there is 1 per cent or more granular cells, the lymphocytes and endothelial leukocytes are being reduced in their absolute numbers. The percentage of reduction can be determined roughly by the percentage of granular cells present after the total count has been lowered to the foregoing figures. With a total count of 1,000 or less, the absolute number of lymphocytes is greatly reduced. The mechanism of the reduction in lymphocytes is obscure, as there is no evidence of the destruction of lymphoid tissue. Only theories can be advanced. If the pathologic changes in the lymph nodes as reported by Hueper and Garrison [29] are present in all cases, they may account for the diminution of lymphocytes.

Endothelial Leukocytes (Monocytes and Transitionals).—These may at first be present in their normal absolute numbers. As the disease becomes more and more severe, there seems to be a depression in reticulo-endothelial tissue, so that the absolute number of endothelial leukocytes becomes much reduced. Some authors report an absolute

increase in endothelial leukocytes at the beginning or during recovery in a case and consider it due to a marked proliferation of the reticulo-endothelial system, particularly in the spleen. Schilling [2] stated that in malignant neutropenia the endothelial leukocytes (monocytes) are greatly increased in contrast to the neutrophils. On the other hand, many authors do not accept as malignant neutropenia any case in which there is a significant absolute increase in either lymphocytes or endothelial leukocytes. When present in normal numbers, their morphology seems to be normal. Conner and his associates [61] reported an increase in the percentage of endothelial leukocytes in three of five patients. Goldenberg [62] reported the case of a patient with two attacks, death occurring in the second. The endothelial leukocytes were highest during the second attack. He said: "This increase of endothelial leukocytes may be interpreted as an extra medullar effort to meet the emergency." The cells, being macrophages, may be interpreted as coming to take up the work of the absent granulocytes. Ferrata [63] said that the cell known as the clasmatocyte, macrophage or reticulo-endothelial type, may elaborate specific granulations in its cytoplasm and become a granulocyte. He found such cells in the blood stream, containing either neutrophilic or eosinophilic granulations, and termed them "hemohistiocytes." If one accepts this theory of Ferrata, then Goldenberg's assumption concerning the increase of these cells is correct. Doan and Sabin [64] have offered another explanation for the "hemohistiocytes," namely, that neutrophilic and eosinophilic granules may be phagocytosed from granulocytes and their débris. Since there is such a scarcity of material to phagocytose in the final stages of this disease, this explanation does not seem to apply.

Türck's Irritation Forms.—There is not any information to be found in the literature concerning these cells in cases of benign and malignant neutropenia. As they appeared in cases of my series, it might be well to include some information concerning them. Schilling [2] said: "They originate partly from the migratory cells of the tissues; they may be found in normal blood at times especially during acute irritations of the marrow or of the lymphatic organs through anemias and leukocytoses; . . . they may be merely functional types of lymphocytes or myeloblasts." In one of my cases, they appeared on the fifth day before death and increased to 11 per cent in the last count made a few hours before death. In another case, the cells ranged from 1 to 7 per cent during the first eight days while the patient was in the acute stage of her illness.

61. Conner, H. M.; Margolis, H. M.; Birkeland, I. W., and Sharp, J. E.: Proc. Staff Meet., Mayo Clin. **6**:193, 1931.

62. Goldenberg, C.: Virginia M. Monthly **58**:391, 1931.

63. Ferrata, A.: Le emopatie, Milan, Italy, Societá editrice libraria, 1918, vol. 1.

64. Doan, C. A., and Sabin, F. R.: J. Exper. Med. **44**:285, 1926.

They were absent during the last five days before discharge from the hospital. In the other cases, they ranged from 1 to 2 per cent. According to the literature, these cells signify only an acute irritation of the bone marrow.

Erythrocytes.—In typical cases the erythrocytes are not affected. If, however, the illness lasts more than the usual ten days, the erythrocytes may be affected and diminished. In fulminating cases the erythrocytes are not affected because there is not time. The erythrocytes and hemoglobin may have been low before the attack, in which case the decrease cannot be said to be due to the neutropenia. This was noted in one of my cases which occurred during the seventh month of gestation, at which time anemia is often found. When anemia is present, it is of the secondary type with erythrocytes more or less achromic and their average diameter less than 7 microns.

Blood Platelets.—Most authors are agreed as to the normal or the increased numbers of blood platelets. They may become reduced if the disease is of fairly long duration and the bone marrow becomes more or less aplastic, but ordinarily the patient dies before this eventuality occurs. In malignant neutropenia (secondary) due to benzene and other drugs the blood platelets are reduced.

Toxicity of the Serum.—Hansen-Prüss [41] carried out studies on the toxicity of the serum in a case of cyclic benign neutropenia. During and before an attack, normal leukocytes of the same blood group mixed with the patient's serum lost their motility and became rounded in forty-five minutes, while several of the previously active motile granulocytes were dissolved. This same serum had no influence on washed lymphocytes or endothelial leukocytes. In a control mixture of type two serum and homologous washed leukocytes, the granulocytes retained their motility for an hour and a half. Hansen-Prüss regrets that he was not able to carry this experimental work as far as he wished so as to prove or disprove the point. Roberts and Kracke [24] performed the following experiment to determine the toxicity of the serum: When their patient's white cells totaled 400, they took 2 cc. of the patient's blood (oxalated) and mixed it with 2 cc. of normal blood of the same type. Two cubic centimeters of normal oxalated blood was mixed with 2 cc. of another normal blood for control. Differential and total white counts were made at two hour intervals for forty-eight hours, but neutrophilic destruction could not be demonstrated. This experiment would demonstrate only the presence of granulocytes, but would not determine if their motility had been destroyed, or whether or not the cells were viable. It is known that some normal serums will be incompatible, that is, will possess specific leukotoxins for the granulocytes of another patient belonging to the same group, and that when oxalate or

citrate is added, the plasma is doubly toxic. Experiments on leukotoxins by Doan [65] show that this factor must be taken into consideration in any experiment to determine the toxicity of the serum. Conner and his co-workers [61] supported the destructive theory of the blood serum in this disease with the fact that in one of their cases, three hours after transfusion there were 300 less white cells. This is not conclusive evidence either, as the limit of error in counting cells (200) is known, and the rhythmic delivery of cells to the blood stream must be taken into consideration. One can, therefore, say that sufficient proof is not at hand concerning the toxicity of the serum in malignant neutropenia.

Blood Cultures.—Many cases have shown positive blood cultures, Streptococcus viridans and haemolyticus, Staphylococcus aureus, Pneumococcus, Bacillus coli and Bacillus pyocyaneus being most frequently found. These blood cultures have not been sufficiently ignored, especially if they occur late in the disease, since the disease is characterized by an early breaking down of the normal protective mechanism. Many cases have had negative blood cultures.

Urine.—The urine in malignant neutropenia is not significant. There may be albumin and casts in varying amounts. The urinary findings would be those expected in any febrile disease.

Cultures and Direct Smears from the Throat and Mouth.—Direct smears from lesions of the mouth many times show Borrelia vincenti (Vincent's organisms), Fusiformis dentium, streptococci, pneumococci and staphylococci. All of these organisms, except Vincent's organisms, appear in the routine cultures. All of these organisms make their appearance sooner or later in most lesions of the mouth, especially in those associated with diseases of the blood. The organisms and their lesions may be considered incidental and secondary. Mucous membranes are normally protected by the granulocytes, which can be found in abundance in these areas. When this normal protective barrier is removed, lesions can be expected, as organisms are always present.

Biopsies on Specimens of Bone Marrow.—These are important in enabling one to study the mechanism of malignant neutropenia while the patient is still alive. Furthermore, biopsy on the fresh specimen of bone marrow is immeasurably superior to the specimen observed at autopsy, even if postmortem examination is done within a few hours after death. Biopsy on the sternal bone marrow is the method par excellence for the exact differentiation between neutropenia with a maturation arrest (normal myeloid tissue, light or marked myeloid hyperplasia), neutropenia with myeloid aplasia and certain other diseases affecting the bone marrow.

65. Doan, C. A.: The Recognition of a Biologic Differentiation in the White Blood Cells, J. A. M. A. **86**:1593 (May 22) 1926.

SYMPTOMS

The patients are wilted in appearance; the skin is pale, but the mucous membranes are of good color. The weakness, marked prostration and toxic appearance are out of all proportion to the few physical signs. Jaundice is rare in typical cases. The liver and spleen may be enlarged. The patients are characterized by weakness, easy fatigue, drowsiness and tendency to infection, especially in the oral cavity. There is evidence that just mere lack of neutrophils will cause such symptoms as fever, weakness, inertia and mental and physical collapse. Roberts and Kracke [28] were among the first to recognize the importance of analyzing accumulated data in reference to the white cell level and the symptomatology. They found that complaints of weakness, exhaustion and fatigue were twice as frequent in the neutropenic patients as in those showing a normal white cell count. Furthermore, the severity of the symptoms paralleled to a remarkable extent the degree of neutropenia found. The fulminating cases are rapid in progress, with a comatose condition usually preceding death. The disease may last from three days to three months, in rare cases a number of years, and end with death or with recovery. The benign cases usually correspond to the fatal group of cases as far as the early symptoms are concerned.

Onset.—Fever, chill and sore throat are the usual mode of onset, which may be sudden or gradual. There may be added to these headache, marked palpitation with a tumultus heart beat, general aching, drowsiness and occasionally delirium. Some patients are nauseated and vomit, and, as a rule, there is dysphagia. There is an offensive, fetid odor to the breath, and the tongue is often heavily coated. According to Roberts and Kracke,[24] there are three onsets: a marrow onset, a blood stream onset and a clinical onset. There is another type with a blood stream onset and a clinical onset, the marrow being normal or hyperplastic.

Fever.—The temperature ranges from 101 to 106 F. and is of the continual type. In mild or chronic cases, the temperature may be normal or only slightly elevated.

Previous Health.—A great many patients give a history of weakness or lack of vitality for varying periods before the onset of the condition, especially in the chronic recurring cases. Some patients state that there was a lack of energy for years and a marked weakness for a few weeks or months before the onset of the acute symptoms. On the other hand, neutropenia occurs in some patients who have always been well and who were active physically and mentally until the sudden onset. These cases are more rare, and it may be that an undetected chronic granulopenia had been present. Occasionally, benign and malignant neutropenia follow in wake of some other disease.

Angina.—It cannot be said that the relationship between neutropenia and stomatitis is quantitative, but it is known that a severe leukopenia, especially a neutropenia, is frequently associated with lesions of the mouth, probably because the oral cavity constantly harbors virulent organisms and its natural barriers are subjected to frequent insults. All patients do not have lesions of the mouth. The unusually good oral hygiene practiced by some patients probably accounts for this.

Local Lesions.—The local lesions seen in benign and malignant neutropenia usually occur on the mucous membranes, more rarely on the skin. Lesions of the mucous membranes when present, are localized mainly in the mouth and involve various structures, such as the gums, tonsils, soft palate, lips, pharynx and buccal mucous surface. More rarely the nose, uterus, vagina, rectum, anus and skin are involved. Local lesions may also occur any place along the gastro-intestinal tract or in the lungs, and the symptoms are according to the areas involved. There may be regional adenopathy with necrosis and sloughing of the overlying tissues and skin. The tonsils, when involved, have in some cases sloughed away.

Character of the Local Lesions.—The local lesions may be inflammatory, with marked edema, ulceromembranous or gangrenous. The areas may slough, and there may be severe hemorrhage from them. The membrane, when present, may be dirty yellow, gray or greenish black.

Clinical Types.—1. Fulminating, acute type, like the cases originally reported by Schultz.[9] The onset is sudden, with a chill, high fever and necrotizing angina; occasionally there may be jaundice, and albuminuria is frequently present. The blood shows an extreme degree of leukopenia and neutropenia, and the bone marrow reveals a widespread necrosis of the granulopoietic system. This type is rapidly fatal. 2. Subacute type, in which the illness is more prolonged. Thompson[66] reported a series of these cases with the following clinical picture: There are several days of fever, followed by a moderate, soft, tender enlargement of the lymph nodes and spleen, accompanied by moderate to extreme leukopenia and a reduction in neutrophils, often reaching an almost complete absence. There is a relative increase in the endothelial leukocytes, and abnormal forms are sometimes seen. Toward the end of the disease the pharynx becomes red and sore, and scattered, round, superficial, whitish spots appear on the posterior pharyngeal wall. The disease lasts from one to three weeks, and with but one possible exception in his series, all of the patients recovered promptly and completely, almost by crisis. 3. Recurring, or relapsing cases. Patients with this type have two, three or more attacks several weeks or months apart. The symptoms during an attack may be similar to those in the

66. Thompson, W. P.: Am. J. M. Sc. **180**:232 (Aug.) 1930.

fulminating or subacute types. Death may occur in the second or third attack; the patients may make a complete recovery, or the process may become subchronic. 4. The subchronic type. In this type the cases begin insidiously. The leukopenia usually is less intense, and the number of granulocytes is higher than in the other types. Some show a high percentage of endothelial leukocytes. There is necrosis of the bone marrow, but it shows an active power of regeneration. The patients may be sick for a year or more and finally recover. Rosenthal [8] reported two subchronic cases in his series which had been under observation for six years. They showed a continuous leukopenia of 1,500 without symptoms, except easy fatigue. 5. Cyclic type. These cases present a chronic, regularly recurring, periodic neutropenia. Only two cases of this type are reported. One of the patients [41] had an attack of neutropenia every three weeks, beginning in 1910, when he was 2½ months old, and these attacks still continued when he was last observed in 1930. The other patient (case 3 [19]), a woman, aged 18, has been studied over a period of more than a year. There recurs in this patient, on the average of from every twenty to twenty-one days, a relative and absolute neutropenia of severe grade, without the appearance of immature cells in the blood and uninfluenced by the administration of pentose nucleotide. This cycle is unassociated with the menstrual history. Occasionally, the five types may be mixed, as subchronic recurring or subacute recurring. These varying types and the degree of severity of the neutropenia may depend on the type and degree of reduction of the maturation factor or the chemotactic factor for granulocytes.

In many patients suffering from an attack of benign or malignant neutropenia pneumonia has developed, and in some typhoid fever. It may have been that the typhoid organisms were in the intestinal tract and the pneumococci in the throat, as in carriers, and as the neutropenia developed, these organisms invaded the unprotected tissues, giving an associated, or secondary, independent infection.

DIAGNOSIS

Neutropenia must be diagnosed early if the mortality is to be reduced. There should be more critical cytologic examinations of the blood, as there is much evidence in the literature that the neutropenia precedes all other symptoms. To wait for the appearance of sore mouth, sore throat, fever and prostration is only giving the army of organisms time for invasion. The patient is ill from several days to several weeks, or perhaps months, before the acute stage in many cases. The history of some cases shows that the patients were treated for a week or more for influenza, sore throat or diphtheria. Diagnosis in a typical case is fairly easy. The symptoms and blood picture are as characteristic as those occurring in pernicious anemia. A typical history is the appear-

ance of sore throat in a middle-aged patient, usually debilitated, accompanied by chills and fever, ulceration and then membrane formation in the throat and on the buccal mucous membrane. If angina is absent, with only fever of more or less long duration and with but few clinical signs, the diagnosis is more difficult. The rule should be to follow up each case of continued fever with frequent leukocyte and differential counts. If angina and fever are both absent and there are only weakness, malaise and drowsiness, a frequent leukocyte and differential count should be made. Since many cases are reported to have followed Vincent's angina and trench mouth, a careful study of the blood should be made in these cases. Other cases have been reported following the extraction of teeth and tonsillectomy, so that a total leukocyte and differential count should precede these operations. The diagnosis is made on the low total count and the neutropenia. Some authors state that normal numbers of circulating erythrocytes and thrombocytes are essential to the diagnosis and do not accept as malignant neutropenia any case in which there is a significant absolute increase in lymphocytes or endothelial leukocytes. A sternal marrow biopsy would aid in the diagnosis and distinguish the aplastic from the hyperplastic type.

DIFFERENTIAL DIAGNOSIS

Acute follicular tonsillitis, Vincent's angina and diphtheria are to be differentiated by appropriate clinical means and a routine leukocyte and differential count. None of the aforementioned disorders causes leukopenia. Gordon and Litvak [67] discussed the differential diagnosis between diphtheria and oral lesions of the blood dyscrasias. Patients with streptococcic sore throat with Streptococcus haemolyticus septicemia occasionally have leukopenia, but rarely less than 5,000 or 4,000 cells, and the differential count usually shows at least 85 per cent neutrophils. In typhoid fever and influenza the total white cell count is rarely less than 4,000, and the neutrophilic percentage is at least 25. Generalized, rapidly advancing tuberculosis may show a marked leukopenia, as low as 3,000 cells, but the neutrophils comprise from 90 to 99 per cent, mostly immature forms. Pneumonia may at times cause leukopenia, rarely below 6,000 cells, and there is always a preponderance of neutrophils. Benign and malignant neutropenia without angina may simulate any febrile disorder associated with leukopenia. A frequent leukocyte and differential count should be made until the diagnosis is established.

Lymphosarcoma.—This condition may cause leukopenia with a reduction in neutrophils. The clinical course will serve to make the diagnosis, and it may be confirmed by the biopsy findings.

67. Gordon, M. B., and Litvak, A. M.: M. J. & Rec. **131**:35 (Jan. 1); 74 (Jan. 15) 1930.

Leukemias.—Benign and malignant neutropenia can be differentiated from lymphatic reactions by the fact that in lymphatic reactions there is an absolute increase in lymphocytes, which replace the neutrophils to make the total leukocyte count normal or increased. The lymphatic reactions there are usually many abnormal lymphoid cells, while in benign and malignant neutropenia most of the lymphocytes are normal. The differential diagnosis between acute leukopenic lymphatic leukemia and malignant neutropenia may be so difficult as to be well nigh impossible. In rapidly developing acute leukemia the leukocytes may fall as low as 1,200 or 2,000. The biopsy on the bone marrow will establish the diagnosis in doubtful cases. In the leukemias there is a crowding of the marrow with lymphoid cells. Chronic leukemia with low values for leukocytes also must be ruled out.

Aplastic Anemias.—In aplastic anemia, the onset of the fever is usually not so abrupt and there are subcutaneous hemorrhages and hemorrhages from mucous membranes. There is aplasia of the bone marrow as a whole, resulting in a yellow marrow which is completely barren of erythrocytes, leukocytes and megakaryocytes. There are leukopenia, neutropenia, thrombocytopenia and rapidly advancing anemia of the hyperchromic type. The color index is irregular. There is a relative increase in lymphocytes. If anemia is present in benign or malignant neutropenia, it is of the secondary type; the erythrocytes are more or less achromic, and their average diameter is less than 7 microns.

Infectious Mononucleosis.—In this disease there occasionally may be seen low values for leukocytes. In this condition, the injection of foreign protein will result in an increase in the circulating neutrophils. The clinical manifestations are usually much less severe than in benign and malignant neutropenia.

Care must be taken, also, to distinguish pernicious anemia in an aplastic phase and metastasis to the bones producing the so-called myelophthisic anemia.

Careful inquiry should be made, also, regarding intoxication from benzene, the administration of arsenicals, especially those of the arsphenamine group, and the use of the roentgen rays, radium and thorium X.

PROGNOSIS

In the beginning, the mortality was reported as 100 per cent. Kastlin,[68] in 1927, reported a mortality of 95 per cent. Friedemann,[69] in 1927, gave the mortality as 92 per cent. Harkins,[69] in 1931, reviewed the literature and stated that up to the date of writing at least one

68. Kastlin, G. J.: Am. J. M. Sc. **173**:799 (June) 1927.

69. Harkins, H. M.: Granulocytopenia and Agranulocytic Angina with Recovery, Arch. Int. Med. **47**:408 (March) 1931.

hundred and fifty cases with twenty-seven recoveries had been reported, the approximate mortality rate being 82 per cent. In 1931, Rosenthal [3] reported a series of twenty-six cases, twelve of fatal malignant neutropenia and fourteen of benign neutropenia, giving a mortality of 46.2 per cent in his series. Many of the fourteen patients who recovered had been under observation for six years. Taussig and Schnoebelen [69a] in a review of three hundred and twenty-eight cases (which included the so-called secondary types), found that the mortality was 75 per cent without special therapy and with miscellaneous forms of treatment; 63 per cent with transfusions of blood, and 53 per cent with roentgen treatment. Jackson and his co-workers [69b] reported a mortality of 30 per cent in fifty-four typical cases of agranulocytic angina in which treatment consisted of nucleotides. It will be seen that since 1927 the reported mortality rate has steadily decreased. The increasing use of blood counts will probably cause the reported mortality rate to continue to decrease. Fulminating cases are rapidly fatal, while recoveries are to be expected in those cases which are more prolonged and milder. Very few patients recover if the total count falls below 1,000. Kracke [44] reported one case in which the leukocytes fell as low as 470 and the patient recovered, only to die in a second attack. Friedemann [60] and others ascribed their recoveries to roentgen treatment. Wyatt [70] reported one case in which the patient recovered after surgical drainage of multiple abscesses. Paroulak [71] reported one case with recovery after repeated transfusions. Many recoveries are reported following nucleotide therapy, the mortality with this form of treatment being the lowest. A great many patients are reported to have recovered without any active treatment. Recoveries and deaths are reported with all forms of treatment. It can be seen that the reduction in mortality cannot be ascribed solely to any one mode of treatment. It seems more probable that the reduction is due to the recognition of more cases, owing to more critical studies of the blood and thereby the inclusion of the more chronic cases in the group. Many authors consider that an absolute increase in endothelial leukocytes has some relationship to the severity of the disease and its prognosis, but there is insufficient evidence in the material collected from reported cases to make this a certainty. In the early stages of the disease, the outcome cannot be determined, as in the cases showing myeloid aplasia it depends entirely on whether maturation of the granulocytes will be resumed. In the

69a. Taussig, A. E., and Schnoebelen, P. C.: Roentgen Treatment of Agranulocytosis, J. A. M. A. **97**:1757 (Dec. 12) 1931.

69b. Jackson, H., Jr.; Parker, F., and Rinehart, J. F.: Am. J. M. Sc. **184**:297, 1932.

70. Wyatt, T. C.: New England J. Med. **199**:525, 1928.

71. Paroulak, J.: Arch. d. mal. du cœur **20**:648, 1922.

cases showing peripheral neutropenia and normal or hyperplastic myeloid tissue, the outcome depends on the resumption of delivery of the cells to the circulation.

TREATMENT

A review of the literature indicates that most authors believe that a specific and satisfactory treatment has not yet been discovered for neutropenia, many believing that recovery, when it does take place, is spontaneous and not influenced by the type of treatment. Many cases are on record in which spontaneous recovery took place in what seemed in the beginning to be a malignant (fatal) case. Such a case was reported by Hamburger,[40b] in a patient with 1,500 white cells and 2 per cent neutrophils. There was a gangrenous area over the most prominent part of a left lateral cervical glandular swelling which sloughed. This patient recovered in four weeks without any active treatment, and was still well five years later. One patient who came under my observation recovered without any active treatment except rest and a diet rich in vitamin B. Also, in many cases in which recovery occurred several types of treatment were used, so that it was impossible to draw decisive conclusions as to the efficacy of the measures that were used, or to say which, if any, was responsible for the cure.

The treatment for this disease must be considered under two headings. First, treatment in the acute cases, which means the employment of an agent that will stimulate maturation of the granulocytes and cause their delivery to the circulating blood in the shortest time possible. The mere absence of granulocytes from the blood stream for seven days is probably incompatible with life, and in a system devoid of granulocytes infection quickly takes place. Second, one must consider the treatment of patients with chronic cases with the object of preventing a recurrence if possible.

Treatment for Local Lesions.—Neutropenia is characterized by an early breaking down of the normal protective mechanism afforded by the neutrophilic granulocytes. With these granulocytes absent, the organisms ever present in and on the body quickly invade. Therefore, infection, local or general, is the most frequent complication of benign and malignant neutropenia. The most frequent local lesions are in the mouth and throat. An antiseptic that will not cause a chemical destruction of the tissue is advised. For local treatment to the oropharyngeal lesions, Hamburger [40b] advised the following: After nourishment, the mouth and throat are sprayed with a saturated solution of potassium chlorate, a compressed air atomizer being used. Following the spraying, each ulcerated area and the gums are swabbed with a solution of copper sulphate, 10 grains (0.65 Gm.) to the ounce. This oral treatment is given as often a five times a day, and less frequently as improvement takes place.

Phlegmonous masses in any locality should not be incised unless absolutely necessary, since no local abscess forms under the existing granulopenic state. After the neutrophilic granulocytes return to the blood stream in sufficient numbers, abscesses may form, and incision and drainage may be instituted if necessary. However, when the neutrophilic granulocytes return, many pathologic conditions will right themselves. Surgical procedures of any type should not be attempted for these patients, as it is dangerous in the presence of a leukopenia, especially a neutropenia. Such a procedure may bring about a sloughing of tissue, as healing cannot take place normally in the presence of a leukopenia and neutropenia. There are cases on record in which necrotizing changes have appeared in the skin at the site of venipuncture.

Miscellaneous Agents Used.—In the past it was thought that an agent introduced subcutaneously which would cause a local abscess would in this way stimulate the production of neutrophilic granulocytes. Turpentine was used for this purpose. Intramuscular injections of milk were given for the foreign protein reaction. Such agents are rarely used now, as they have not been shown to have any therapeutic value. Intravenous injections of gentian violet and acriflavine have been given, but they will not stimulate the production of granulocytes. Perhaps they were used with the idea in mind that there was an infection of the blood stream. Fetal liver and extract of bone marrow have been administered, but no definite results have been attributed to them. Squibbs leukocytic extract, in daily intramuscular injections of 50 cc., divided into two doses, has been used in many cases along with transfusions and other forms of therapy. Definite and gratifying results from the aforementioned agents were lacking, and they are rarely used now.

Preventive Treatment.—There is little definite information available as to the management of chronic cases and the prevention of recurrence of acute attacks. Roberts and Kracke [28] made a statistical study of eight thousand records of leukocyte and differential counts from a series of ambulatory patients seen between 1920 and 1930. Their study points out many interesting facts. In the granulopenic group of this series, the count ranged from 4,000 down to 1,000. There were one thousand eight hundred and eighty-one patients with a granulopenia, or one of every four. This number is significant, since benign and malignant neutropenia develop chiefly in patients with granulopenia. In this group the chief complaint was weakness. The evidence accumulated indicates that weakness, exhaustion, fatigue and tendency to sleep are the chief results of a depressed granulocyte count. Patients who have had more than one or two attacks know by their feelings when granulopenia is present. A great many patients give a history of great mental stress or emotional shock. A number of patients with chronic cases improve with rest. Roberts and Kracke, in their series, reported two

such cases; one patient, a man, improved during 1931, business being so poor he had rested more than usual; the other, a physician, improved after retirement, but the condition left him with a loss of 30 pounds (13.6 Kg.) that he never regained and myocarditis. Just in what manner the granulopenia affects the heart is not clear, but arrhythmia, tachycardia and tumultus heart beat are recorded in many cases. This makes it appear essential that patients with granulopenia rest in bed until the granulocytes approach normal. From the foregoing, then, it can be said that rest and freedom from mental and emotional stress should be advised. It would also seem advisable that such patients should refrain from using any drugs shown to have a depressing effect on the granulopoietic tissue, such as those containing the benzene ring. It would be advisable, also, to attempt to clear up all foci of infection, being especially solicitous concerning oral hygiene; in fact, the most scrupulous general hygiene should be observed. A generous allowance of vitamin B should be included in the diet. Operative procedures on these patients should be approached with considerable caution, as the granulopenic state may develop at any time and prevent proper healing. Routine blood counts should be studied with great care, and all patients having a granulopenia should be under careful observation and frequent blood counts should be made.

Diet.—Diet may play a more important rôle both in etiology and in treatment than is now imagined. Doan,[72] experimenting with pigeons by underfeeding, reduced the red marrow of the radius to an extreme hypoplasia. There were only three component parts left: blood vessels, fat cells and a minimal residual framework of reticulum and reticular cells. Lossen[73] made counts of the total number of cells per cubic millimeter in children's marrow, finding that their number seemed, in a general way, to be dependent on the state of nutrition. If this can be proved and the dietary factor that has a specific influence found, it will have a most practical bearing. If, as Minot has suggested, a diet rich in vitamin B is of material aid, especially in the chronic, recurring and cyclic cases, the diet should contain a liberal supply of the following, arranged in order of vitamin content:

Excellent * * * Asparagus; kidney, navy and soy beans; raw cabbage; raw tomatoes; wheat germ.

Good * * * * Heart; liver; kidney; egg yolk; milk; whole cereals; green vegetables; fresh fruit juices.

Fair * * * * Lean muscle meat.

A patient with recurring benign neutropenia, in a series of cases to be reported later, received the following daily diet during a first and

72. Doan, C. A.: Bull. Johns Hopkins Hosp. **33**:222, 1922; Contrib. Embryol. **14**:27, 1922.

73. Lossen, J.: Virchows Arch. f. path. Anat. **200**:258, 1920.

second attack: four egg yolks in milk (chocolate flavored), 750 cc.; tomato juice, 500 cc.; orange juice, 750 cc.; grape juice, 250 cc.; purée of pea soup, 250 cc. As soon as the patient was able to take more solid food, creamed asparagus and cooked oatmeal were added to the list. The patient gained 6 pounds (2.7 Kg.) on this diet during two weeks in bed. This diet and local treatment of the mouth and throat were the only therapeutic measures used in this case.

Treatment of Benign and Malignant Neutropenia Due to Arsphenamine.—Foster [74] successfully treated patients with "malignant" neutropenia due to arsphenamine by the intravenous use of sodium thiosulphate. Kennedy [75] and O'Leary and Conner [76] reported a similar success. The best results are to be had from the intravenous administration of sodium thiosulphate, although it can be given by mouth. McBride and Dennie [77] advised that it be given in not more than 20 cc. of distilled water, with daily intravenous injections for four days, and then alternate days, for as many injections as may be necessary, in doses starting with 0.3 Gm. and increasing by 0.15 Gm. daily. Sodium thiosulphate is nontoxic in doses up to 2 Gm. Dodd and Wilkinson [78] said that there is no specific or stimulating action attributed to transfusion in these cases. Moore and Keidel [79] called attention to the appearance of prodromal or warning symptoms in these patients. They are manifested by itching, mild rash, prolonged fever, malaise or any tendency toward purpura. These authors examined the blood in several cases showing such symptoms and discovered a slight decrease in the neutrophilic cells, an eosinophilia varying from 5 to 8 per cent, a slight increase in the endothelial leukocytes and the presence of numerous fragile leukocytes.

Splenectomy.—Splenectomy was performed in one case reported by Baldridge and Needles.[8] The patient died thirty-five days after the operation. There was not the usual rise of leukocytes after the operation seen in other cases, but there was the usual platelet response. At necropsy the bone marrow showed an overgrowth of myelocytes and myeloblasts almost as marked as in myelogenous leukemia. The authors commented that it was unfortunate that a biopsy specimen of the bone marrow was not obtained before splenectomy, because the part played by the splenectomy in this overgrowth of myeloid cells could have been determined.

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74. Foster, J. M., Jr.: Colorado Med. **27**:388 (Oct.) 1930.

75. Kennedy, W. R.: Canad. M. A. J. **19**:439, 1928.

76. O'Leary, P. A., and Conner, H. M.: Am. J. Syph. **9**:262, 1925.

77. McBride, W. L., and Dennie, C. C.: Treatment of Arsphenamin Dermatitis, Mercurial Poisoning and Lead Intoxication, J. A. M. A. **83**:2082 (Dec. 27) 1924.

78. Dodd, K., and Wilkinson, S. J.: Severe Granulocytic Aplasia of the Bone Marrow, J. A. M. A. **90**:663 (March 3) 1928.

79. Moore, J. E., and Keidel, A.: Stomatitis and Aplastic Anemia Due to Neo-Arsphenamine, Arch. Dermat. & Syph. **4**:169 (Aug.) 1921.

Transfusions.—Transfusions have been used in many of the cases reported, some of the patients recovering and others dying. Transfusion is essentially empirical. No definite conclusions as to its efficacy can be drawn from my experience or from the literature. In practically all of the cases, other measures were used along with the transfusions. It is an established fact that repeated transfusions lower the rate of erythropiesis,[14] and perhaps granulopoiesis. There is no evidence that transfusions actually stimulate granulopoiesis or that the neutrophils added in 500 cc. of blood would be of any assistance, as the life of the neutrophil is short (five days), and the number added would be quite small compared to the number needed. In case 2 of a series of cases reported by Conner and his associates [61] it is pointed out that three hours after transfusion their patient had 300 less white cells. Taking into consideration the limit of error in counting and the rhythmic delivery of granulocytes to the blood stream, it is at least evident that there was not an increase. In case 13 of a series of cases reported by Jackson and his co-workers [80] transfusion was followed by a reduction in white blood cells. The patient in case 16 of the same series was given a transfusion after nucleotides had caused an increase of white cells to start, and there followed a reduction in white cells. Such a reduction of white cells was not seen in the other patients treated with nucleotides alone, after a rise had started. Apparently the rate of granulopoiesis was lowered in this patient by the transfusion. The blood from a healthy donor may contain the principles to bring about normal maturation, but the amount of this substance added to the recipient also would be too small compared to the amount needed.

Immunotransfusion.—In June, 1930, Fisher [81] reported the successful treatment of a patient with "malignant" neutropenia by immunotransfusion. The patient was a nurse, aged 24, who had suffered with sore gums and malaise for two weeks. As Vincent's organisms were found on the gums, she was given 0.4 Gm. of neoarsphenamine intravenously. The next day she was much worse; sore throat developed, and she was admitted to the hospital. The white cells totaled 1,200, with 6 per cent granulocytes. The second and third days she was treated with an ordinary transfusion of 500 cc. of unmodified blood, 25,000,000 dead typhoid germs and an ampule of sodium nucleate. There was no improvement in the symptoms or the blood picture. On the fourth day of her illness, a donor of the same group, who had recovered from this disease in 1927, was secured, and 500 cc. of his blood was given to the patient. The third day after this transfusion,

80. Jackson, H., Jr.; Parker, F., Jr.; Rinehart, J. F., and Taylor, F. H. L.: Studies of Diseases of the Lymphoid and Myeloid Tissues: VI. The Treatment of Malignant Neutropenia with Pentose Nucleotides, J. A. M. A. **97**:1436 (Nov. 14) 1931.

81. Fisher, R. L.: J. Michigan M. Soc. **29**:435 (June) 1930.

or seven days after the diagnosis had been made, the total count was 7,800, and there were 21 per cent granulocytes. (In a spontaneous recovery, improvement occurs at about this time also.) In November, 1930, Harkins [69] also treated a patient with "malignant" neutropenia successfully by giving a transfusion of 500 cc. of blood from a patient who had recovered from this disease. No definite conclusions can be drawn from two cases. There is not any evidence so far to indicate that any kind of immune bodies are formed in the blood stream in this disease. If a recovered patient's serum contained immune bodies, relapses and recurrences should not be the rule. One attack does not give immunity from further attacks. It does not seem advisable to put a strain on the blood-forming tissues of any patient who has had an attack of such a fatal disease. One would not use a patient who had pernicious anemia as a donor for a recipient who had the same disease.

Transfusions and Neoarsphenamine.—The practice of adding neoarsphenamine to the transfused blood now does not seem wise, as Farley [80] reviewed from the literature thirty-nine cases in which the function of the bone marrow was depressed following the use of various preparations of arsphenamine. The symptoms varied from those of purpura hemorrhagica to those of severe aplastic anemia and malignant neutropenia, depending on whether the principal effect was on the granulopoietic, megakaryopoietic or erythropoietic tissue, or on all of these combined.

Irradiation of Bones.—This treatment was first suggested by Friedemann.[60] He applied, in measured amounts, one twentieth of an erythema dose of roentgen rays to the bones of the skeleton, using a hard filter (6 mm. of copper). He irradiated the long bones in four cases, giving from one to three treatments at intervals of from two to several days. He reported that improvement from roentgen treatment may begin within from twenty-four to thirty-six hours, both in the symptoms and in the blood picture. Regarding the dosage, he said that no definite judgment can be rendered. One irradiation with one-twentieth skin unit dose may produce a blood crisis in one patient, and in another it may take three doses to produce a change in the blood picture. In 1930, Friedemann and Elkeles [82] published another article on roentgen treatment of this disease. The first patient given roentgen rays in this country was treated by Call and his associates,[83] and the technic given by Friedemann was used. Waters and Firor [84] reported the cases of five patients treated with roentgen rays; four are still living, and one

82. Friedemann, U., and Elkeles, A.: Deutsche med. Wchnschr. **56**:947 (June 6) 1930.

83. Call, M.; Gray, B. H., and Hodges, F. M.: Am. J. Roentgenol. **20**:550 (Dec.) 1928.

84. Waters, C. A., and Firor, W. B.: Bull. Johns Hopkins Hosp. **48**:349, 1931.

was moribund when first seen. Their technic was as follows: The lower extremities, the pelvis, the upper part of the humeri and the shoulder girdles were irradiated in the course of three or four treatments. Voltage values of 200,000 with aluminum and copper filtration, both separately and combined, with effective wavelengths ranging from 0.197 to 0.161 angstrom units, were used. The measurement of dosage was effected by a dosimeter reading in roentgens, 600 units being adopted as the erythema dose, which was that agreed on at the International Conference of Radiologists at Stockholm in 1928. When such a small dose is to be used, an accurate determination is imperative. Fiessinger and his co-workers [85] reported that roentgen therapy may, under certain circumstances, provoke an "agranulocytic syndrome"; they reported one case. Potter [86] reported a case which in the first stage gave the clinical and laboratory picture of malignant neutropenia, and he stated that it terminated with the picture of myelogenous leukemia, although, judging from the laboratory reports, it was a lymphatic leukemia. It is known that lymphocytes are more easily stimulated by roentgen rays than the granulocytes. This patient was given seven irradiations of one-half erythema dose each, which is a much greater dose than that prescribed by Friedemann. Neidhardt [87] reported the treatment of a patient with a severe case with the roentgen rays. He used one twentieth of the erythema dose. Two hours after the treatment the cells rose from 500 to 800; eight hours later, to 1,700, and the second day, to 3,800. A second treatment was given, and eight hours later the total cells were 9,200. The granular cells steadily increased, and the clinical condition improved. Aubertin and Lévy [30b] said, concerning roentgen treatment: "The efficacy of radio-therapy does not appear doubtful, but it would be well to wait for further observations to appreciate its true value and to fix the rules of its application." Certainly, the attempt should be made promptly to influence this disease by the expert application of the roentgen rays, as, when expertly applied, they at least cannot harm the patient.

Rationale of Roentgen Treatment.—In the adult, the marrow in the shafts of the long bones is mostly adipose tissue, having little or no blood-forming function. When excessive or pathologic demand exists, there is a formation of new centers by differentiation of the myeloblasts into granular myelocytes, the adipose tissue of the bone marrow being replaced by this newly formed tissue. One theory is that irradiation may aid in the formation of this new tissue. The only way of proving just what effect, if any, the roentgen ray has directly on the yellow marrow would be through biopsy as soon as the young granulocytes

85. Fiessinger, N.; Decourt, P., and Laur, C. M.: Sang **5**:257, 1931.
86. Potter H. W.: Virginia M. Monthly **58**:739 (Feb.) 1932.
87. Neidhardt, K.: München. med. Wchnschr. **78**:711 (April 24) 1931.

were appearing in the blood stream. Some investigators say that one cannot be sure whether the apparent stimulation is the result of chemical changes in the blood or is due to the roentgen ray itself, or whether the recovery is spontaneous. Certainly, there is no evidence that a cell per se is affected by the roentgen ray other than in a destructive manner. Friedemann [60] said: "It is evidently essential that as large a surface of the body as possible be subjected to irradiation. Whether, thereby, a direct effect is exerted upon the bone marrow, or an indirect effect by the irradiation of other tissues is also an open question." Also, the effect of the roentgen ray may be indirect, stimulating organs of internal secretion to produce maturation products for granulocytes. Doan's [19] theory is that the roentgen ray benefits the type of case showing peripheral neutropenia with hyperplastic myeloid tissue. The roentgen ray in these cases brings about a primary destruction of some of the intact myeloid foci with a liberation of autogenous nucleotide, which then initiates the maturation and delivery of granulocytes from the remaining myeloid foci. From a review of the literature and following the results in the case reported by Call and his associates,[83] it appears that the roentgen ray might have an important rôle in the stimulation of the granulopoietic tissue, but definite proof is lacking.

Nucleotide Therapy.—The nucleic acids of the animal body occur mainly in combination with protein material in the so-called nucleoproteins of which they form the characteristic radicles. The amount and character of the protein with which the nucleic acid molecule is combined vary, and the acid may, in certain cases, be found in cells in a free form. Those tissues are richest in nucleic acid which contain the largest amount of nuclear material and of nucleoprotein, such as glandular tissue, thymus, spleen, liver and hematopoietic tissue. The nucleic acids are a distinct class of substances, characterized by their decomposition products. Nucleic acids on hydrolysis yield the purine and pyrimidine nucleotides. The purine nucleotides on further hydrolysis finally yield the purine bases, adenine and guanine.

The first work done on the nature of leukocytosis produced by nucleinic acid was by Ames and Huntley.[55b] Jackson [55c] was the first to demonstrate that pentose nucleotide existed in normal human blood. This substance is known to exist principally in the nuclei of living cells. Doan and his co-workers,[18] in their experimental work with large doses of nucleic acid, showed clearly its chemotactic effect. They also found that with nucleic acid there was a leukopenia preceding the leukocytosis, owing to a temporary storage of the granulocytes in the spleen. Then they found that the granulocytes could be called from the marrow by the split products of nucleic acid, adenine and guanine, and that after giving these substances the leukocytes were not withdrawn from the circulation by the spleen, so that there was a direct leukocytosis without

the temporary leukopenia. Reznikoff [88] reported four cases of malignant neutropenia, in three of which the patients recovered following treatment with nucleotides. This investigator actually used purine bases, a decomposition product of nucleotides, as he himself pointed out in a later issue of the same journal.[89] These substances, given intravenously to rabbits, caused a marked increase in the number of neutrophilic granulocytes without any effect on the temperature or any other cells. Adenine sulphate or guanine hydrochloride obtained from the Eastman Kodak Company was used. Other therapeutic agents were used along with this, so no precise conclusions can be drawn. Jackson and his associates,[80] in their series of cases, used the unbroken pentose nucleotide, called nucleotide K-96, which is prepared by Smith, Kline and French Company, according to the technic of Jones and Perkins [90] and under the direction of the Harvard Medical School. Twenty patients were treated. Thirteen had "malignant" neutropenia, five leukopenia and neutropenia due to an infection, and two benzene poisoning. Of the thirteen patients with "malignant" neutropenia treated, seven recovered. The first sign of improvement occurred between the third and seventh day, usually on the fifth day. The total and differential counts were invariably normal in ten days, sometimes in eight. They commented: "The consistency with which the reaction occurred on or about the fifth day is of great significance. It is at this time that the reticulocyte rise begins to take place following liver therapy in pernicious anemia." This reaction would tend to show that the time for the maturation of the granulocytes is about the same as that of the erythrocytes. There is no definite experimental proof, however, that nucleotide K-96 supplies a maturation factor for granulocytes. Doan,[91] experimenting on normal rabbits with pentose nucleotide, produced not only an extensive degree of myeloid hyperplasia, but also an extramedullary myelopoiesis in the kidneys and spleen. This, however, is the action of pentose nucleotide on a normal marrow. This hyperplasia may be a "replacement reaction" due to the chemotactic action (normally, the calling out of cells stimulates replacement), and just what effect pentose nucleotide would have on a marrow rapidly becoming exhausted or aplastic is not known. Five of the patients with malignant neutropenia in this series [80] died in spite of active nucleotide therapy. This result recalls the possible difference between the pathology of benign neutropenia and of malignant neutropenia; i. e., the function of granulopoiesis was depressed, maturation had ceased, and the bone marrow was aplastic in the fatal cases, while in the benign cases of neutropenia, the function of granulopoiesis was arrested, maturation

88. Reznikoff, P.: J. Clin. Investigation **9**:381 (Dec.) 1930.
89. Reznikoff, P.: J. Clin. Investigation **9**:555 (Feb.) 1931.
90. Jones, W., and Perkins, M. E.: J. Biol. Chem. **62**:559 (Jan.) 1925.
91. Doan, A. C.: Proc. Soc. Exper. Biol. & Med. **29**:1030, 1932.

had not ceased, and the bone marrow was not exhausted but was normal or hyperplastic, the chief fault seeming to have been in the delivery or lack of a chemotactic factor. It seems only reasonable to assume that if the cells are not developing they cannot be called to the circulation. The patients with acute cases in Jackson's series were given 0.7 Gm. of nucleotide K-96 in 100 cc. of saline solution intravenously daily for four days, and 0.7 Gm. in 10 cc. of distilled water, given in addition intramuscularly, on the same days and on each day subsequently until there was definite improvement. The intramuscular injections usually cause no reactions; the intravenous injections cause a sharp, temporary reaction at times. Jackson and his co-workers concluded: "We believe that these nucleotides may have a definitely favorable effect on the average inactive bone marrow and in certain cases of malignant neutropenia, and we believe that the substance is worth further trial in such cases."

Calcium Gluconate.—Hare and Childrey [92] reported a case of malignant neutropenia in a patient whose symptoms suggested a disturbance of the calcium metabolism. Calcium gluconate was administered, and granulocytes appeared in the blood on the fifth day following treatment. This suggested to the authors that this agent may be of therapeutic value.

SUMMARY

1. The subject of benign and malignant neutropenia has been covered, and this information has been compiled in more or less textbook fashion.

2. Many names have been proposed for this disease entity, benign and malignant neutropenia seeming to be the most appropriate.

3. The two groups, benign neutropenia and malignant neutropenia, have been further subdivided into primary and secondary groups, depending on the etiology. A classification is based on this method of distinction and on the clinical course, which tends to give a mental picture of the types that make up this disease.

4. A review of the physiology of granulopoiesis is given, since the accuracy in interpreting the blood picture in primary benign and malignant neutropenia is dependent on an understanding of the underlying mechanism of granulopoiesis.

5. A review of the theories of pathogenesis of benign and malignant neutropenia is covered, and a theory is formulated based on the underlying pathology and physiology of granulopoiesis. It is suggested that in each case of neutropenia it would be advisable to determine the etiology and underlying changes in the bone marrow. Biopsies on speci-

92. Hare, R. A., and Childrey, J. H.: Treatment of Agranulocytic Angina with Calcium Gluconate, J. A. M. A. **98**:2277 (June 25) 1932.

mens of bone marrow in all cases before treatment is begun would prove or disprove the theory of an endogenous disturbance of chemotactic and maturation factors for granulocytes as being the cause of this disease.

6. The pathology of the characteristic lesions has been covered, and complete laboratory data given.

7. Symptoms, diagnosis, differential diagnosis and prognosis have been discussed.

8. A section is devoted to a theoretical consideration of the treatment for this disease, as well as a review of all forms of treatment to be found in the literature. The rationale of these treatments, when possible, has been discussed. The theory is advanced that a specific treatment for malignant neutropenia involves an investigation of the chemical maturation factors which determine the granulocytes.

REPORT OF CASES

I wish to report four cases: two cases of primary malignant neutropenia as described by Schultz;[9] one of primary subchronic recurring benign neutropenia, and one which began as a fulminating case, with recovery, and three months later recurred as a primary subchronic benign neutropenia. This classification is taken from a previous article.[93] The cases came under my observation at Stuart Circle Hospital in the past four years; one, case 3, was reported by Richardson;[94] one, case 1, was reported by Call and his associates.[55] Further studies have been made in case 1 since the first report.

CASE 1.—A white woman, aged 27, an American, married, eight months' pregnant and the mother of two children, was taken ill on Oct. 19, 1928, complaining of pain in the right side of the abdomen and giving all the symptoms of pyelitis. On October 20, there was a slight sore throat, which progressively became worse on the twenty-first and twenty-second. The patient entered the hospital on October 23, with the following symptoms: The larynx, nasopharynx, faucial pillars and tonsillar fossae were acutely inflamed; the gums were sore and painful, with numerous erosions; there were general malaise, slight chills and drowsiness; she had an anemic appearance; the temperature was 100.2 F.; the pulse rate, 130; there was a loss of weight of 11 pounds (5 Kg.). The spleen was not palpable, and there were no glandular enlargements. The tonsils had been removed five years previously. The present pregnancy had been normal, with only an occasional headache and some indigestion. The leukocyte and differential count made on admission showed a marked leukopenia and neutropenia, which confirmed the diagnosis (table 1). There was also marked anemia; the erythrocytes numbered 2,450,000; the hemoglobin, by the Newcomer method, was 8.45 Gm. (50 per cent). This type of anemia is frequently seen in the latter months of pregnancy. A direct smear from the throat showed streptococci; a culture showed staphylococci with streptococci predominating. Smears from the gums showed streptococci and Vincent's

93. Beck, Regena C.: Bull. Stuart Circle Hosp. **2**:41 (Aug.) 1932.
94. Richardson, J. K.: Virginia M. Monthly **58**:545 (Nov.) 1931.

organisms. Blood cultures made on October 23 and 29 were negative. Urinalyses made throughout the course of the disease were negative except for a trace of albumin.

On October 23, the patient was given a transfusion of 250 cc. of blood, and on October 24, 350 cc. of blood. The symptoms and blood picture had grown progressively worse during October 23 and 24, the total leukocytes on the twenty-fourth being 640. The patient was desperately ill; the cervical lymph glands were enlarged; large plugs of mucus and membrane were being discharged from the nose, and there was blood-streaked, frothy sputum. Fetal movements had ceased; the fetal heart could not be heard, and the baby was thought to be dead. On October 25, decision was made to try roentgen treatments as prescribed by Friedemann.[62] (This was the first patient to be treated by this method in this country.) One-twentieth of an erythema dose, using a 6 mm. aluminum filter and a distance of 50 cc., was used for two minutes over the lower extremities and over the throat. A slight improvement was noted in the blood picture on the morning of October 26, more especially in the neutrophils; by evening this improvement was quite marked, the neutrophilic granular cells having risen from 21 to 53 per cent. The total number had increased only from 700 to 875. Fetal movements returned, and the fetal heart could be heard. From October 26 to 30, improvement in the symptoms and blood picture was slow but steady, the temperature dropping to normal on October 29. On October 30, it was felt that a second roentgen treatment could be given, and it was applied over the upper extremities, and one additional minute was repeated over the femurs. On November 1, a third roentgen treatment was given. From October 30 to November 17, improvement was marked. The only treatment other than roentgen used after October 25 was supportive, with local treatment to the throat and mouth. The patient was discharged on November 17 feeling well and with a normal leukocyte and differential count; the erythrocytes numbered 3,400,000, and the hemoglobin was 9.97 Gm. (59 per cent).

On November 27, the patient entered the hospital for delivery. The next morning labor was induced. She was delivered on the afternoon of November 29 of a male child, weighing 6 pounds (2.7 Kg.) and in good condition. After delivery, the spleen was found to be 3 inches (7.6 cm.) below the costal arch, but was not sensitive, and it decreased in size in a few days. Beginning on the first day after delivery and lasting until the seventeenth day, the patient had a septic temperature, which was as high as 102 F. Blood cultures made on December 12, 15 and 28 were negative. The blood sugar was 92 mg. per hundred cubic centimeters; urinalyses gave negative results. All during this second period in the hospital the patient's lowest total count was 4,450; the lowest neutrophilic granular percentage was 26. Because of this low percentage of granular cells, another roentgen treatment was given to the long bones on December 12. The patient was discharged from the hospital on Jan. 1, 1929, with a normal blood picture and feeling well. The total erythrocytes were 3,990,000; the hemoglobin was 12.17 Gm. (72 per cent).

On January 25, the patient's total leukocytes were 4,600. On this date we tried out the hemoclastic crisis test of Widal. Two hundred cubic centimeters of milk was given on an empty stomach, and instead of the usual leukocytosis (leukocytosis developed in a normal control patient), there was a marked leukopenia (table 1). Just what the significance of this reaction is in this disease cannot be stated.

On February 12, a marked leukopenia again developed, and the patient entered the hospital for her fifth roentgen treatment, observation and study of the blood. At this time the blood culture was negative; the blood chlorides were 528 mg.;

TABLE 1.—*Blood Count in Case 1**

Date	Total White Cells	Myelo-blasts	Myelo-cytes	Juvenile Cells	Seg-mented Cells	Lympho-cytes	Endo-thelial Leuko-cytes	Other Cells	Undif-feren-tiated Cells
10/23/28	1,400	..	1	..	15	72	8	3 Türck	1
10/23/28	1,200	..	1	13	10	76			
10/24/28	1,025	..	4	4	7	81	2	1 Türck	1
10/24/28	640	..	..	14	14	60	12		
10/25/28	700	..	..	7	14	77	..	1 Türck	1
10/25/28	First roentgen treatment given								
10/25/28	733.5	..	..	..	11.5	69.5	4.5		
10/26/28	850	..	1.4	8.5	17.5	69	2.6	1 Türck	1
10/26/28	875	..	8	20	25	36	7	.....	4
10/27/28	1,050	..	1	9	36	49	2	2 Türck	1
10/27/28	750	..	6	11	26	47	6	.....	4
10/28/28	1,100	..	7	6	24	58	2	.....	3
10/29/28	1,150	..	2	10	39.5	39.5	6	2 Türck	1
10/30/28	1,713	..	4	12	34	39	2	7 Türck	2
10/30/28	Second roentgen treatment given								
10/31/28	2,825	..	1	10	39	46	2	1 Türck	2
11/ 1/28	2,980	..	1	9	49	39	1	2 Türck	2
11/ 1/28	Third roentgen treatment given								
11/ 2/28	3,225	..	1	7	53	37	2		
11/ 3/28	3,244	..	1	4.5	64.5	27.5	..	.....	0.5
11/ 5/28	5,800	..	..	4	73	22	..	1 Türck	
11/ 7/28	6,300	..	..	2.5	77	18.5	0.5	0.5 Türck	
11/ 9/28	6,750	..	..	2	79	17	2		
11/10/28	7,700	..	..	..	83	16	..	.....	1
11/12/28	8,850	..	..	..	86	13	1		
11/14/28	8,400	..	1	..	82	17			
11/16/28	7,025	..	..	..	85.5	14.5			
	Discharged from hospital								
11/24/28	4,431	2	2	..	73	23			
11/27/28	5,600	..	1	..	73	23	..	1 Türck	2
	Entered hospital for delivery								
11/30/28	4,750	1	1	..	64	32	1	.....	1
12/ 1/28	4,900	4	3	..	63	28	..	.....	2
12/ 3/28	4,500	..	3	1	45	46	1	.....	4
12/ 4/28	5,400	2	2	1	53	39	..	1 Türck	2
12/ 5/28	6,300	4	..	..	51	44	..	.....	1
12/ 6/28	6,700	1	..	..	52	43	1	1 Türck	2
12/ 7/28	7,300	1	..	1	63	31	..	1 Türck	1
12/ 8/28	7,300	1	..	..	49	49	1		
12/10/28	6,500	..	..	..	45	54	..	.....	1
12/11/28	5,950	1	..	..	33	62	4		
12/12/28	Fourth roentgen treatment given								
12/12/28	6,400	..	..	..	24	75.5	..	.....	1.5
12/13/28	7,750	..	..	11	15	71	2	.....	1
12/14/28	4,450	..	..	9	36	53	2		
12/14/28	4,450	..	3	18	22	62			
12/15/28	4,800	..	..	8	21	64	5	1 Türck	1
12/17/28	4,800	..	..	4	34	60	2		
12/18/28	5,400	..	..	4	24	69	3		
12/19/28	5,250	..	..	2	56	39	3		
12/20/28	4,600	..	..	4	44	50	2		
12/21/28	4,900	..	..	3	46	49	2		
12/22/28	5,600	..	..	..	44	53	3		
12/24/28	7,600	..	..	1	68	30	1		
12/26/28	7,200	..	..	2	54	42	2		
12/28/28	7,600	..	..	1	64	35			
12/31/28	6,500	..	..	1	60	38	..	1 Türck	
12/31/28	Discharged from hospital								
1/10/29	6,600	..	..	..	50	50			
1/18/29	5,650	..	..	5	31	64			
1/25/29	4,600	..	..	..	33	59	7	1 eosinophil	
1 hr. later	3,400	..	..	..	39	59	1	.....	1
2 hrs. later	4,100	Hemoclastic crisis test			30	69	1		
Third hr.	3,700	..	..	16	29	52	..	1 Türck	2
1/29/29	4,000	..	..	..	32	67	1		
2/ 5/29	4,200	..	..	..	27	73			
2/12/29	Entered hospital; fifth roentgen treatment given								
2/12/29	2,600	..	1	21	18	58	2		
2/13/29	2,400	..	..	8	14	78			
2/14/29	2,900	..	2	3	21	71	..	1 Türck	1
2/15/29	4,200	..	..	5	28	65	..	.....	2
2/16/29	3,400	..	..	4	18	77	..	.....	1
2/18/29	3,933	..	..	2	39	56	2	.....	1
2/19/29	3,100	..	..	7	49	42	..	.....	2
2/20/29	2,800	..	..	5	46	46	1	.....	2
2/21/29	3,400	..	..	..	49	51			

* Where two counts appear on the same date, the first was made at 9 a. m. and the second at 4 p. m.

TABLE 1.—*Blood Count in Case 1—Continued*

Date	Total White Cells	Myelo-blasts	Myelo-cytes	Juvenile Cells	Segmented Cells	Lympho-cytes	Endothelial Leuko-cytes	Other Cells	Undifferentiated Cells
2/22/29	3,200	..	..	4	47	48	1		
2/23/29	4,100	..	..	5	27	65	..	2 Türck	1
2/25/29	2,600	..	..	7	59	34			
2/26/29	3,800	..	..	..	45	54	..	1 Türck	
2/27/29	4,000	..	..	..	43	57			
2/28/29	4,450	..	..	..	48	53			
3/ 1/29	3,900	..	..	..	54	46			
	Discharged from hospital								
3/ 5/29	3,700	..	..	5	54	41			
3/ 8/29	3,500	..	..	..	38	60	..	.....	2
3/14/29	1,400	..	..	5	19	76			
3/14/29	Sixth roentgen treatment given								
3/16/29	1,500	..	..	3	29	67	..	.....	1
3/18/29	1,650	..	..	2	26	71	1		
3/21/29	2,450	..	..	2	50	48			
3/28/29	2,200	..	1	10	31	54	2	.....	2
4/ 2/29	1,450	..	..	5	29	65	..	.....	1
4/ 4/29	1,600	..	..	4	13	81	2		
4/ 5/29	1,463	..	..	11	14	72	..	.....	3
4/ 9/29	2,250	..	..	4	26	70			
4/12/29	2,537	..	..	7	39	54			
4/15/29	3,500	..	..	5	38	51	..	.....	6
4/18/29	1,850	..	..	10	38	48	..	.....	4
4/22/29	2,012	..	..	8	66	22	3	.....	1
4/27/29	2,500	..	..	..	38	62			
6/ 5/29	4,800	..	..	..	62	37	1		
6/13/29	5,800	..	..	..	70	28	2		
6/22/29	Entered hospital; diagnosis: abscess of thigh								
6/22/29	1,000	..	1	11	31	53	..	.....	4
6/24/29	2,300	..	..	11	38	47	..	.....	4
6/24/29	Discharged from hospital								
7/16/29	2,800	..	..	2	36	54	..	2 Türck	6
8/ 6/29	4,450	..	..	..	63	37			
3/20/30	8,100	..	..	..	57	42	..	1 eosinophil	
4/17/30	6,250	..	..	..	71	29			
2/ 2/31	5,075	..	..	..	64	34	1	1 eosinophil	

the carbon dioxide-combining power was 72.1. The temperature was normal, and she felt well, the only complaint being fatigue when neutropenia was present. The blood picture improved during this period in the hospital, but on March 1, when she was discharged, there were still moderate leukopenia and neutropenia.

On March 14, the total white cells were 1,400, with 24 per cent neutrophilic granular cells. On this date the patient received her sixth and last roentgen exposure, but the blood picture did not reach normal until June 13.

The patient was admitted to the hospital again on June 22 with the diagnosis of abscess of the thigh in the gluteal region. Her temperature was 100.8 F. on admission, and was normal when she was discharged on June 24. The total white cell count at this time was 1,000, with 43 per cent neutrophilic granular cells. The patient felt well except for the local discomfort.

Periods of leukopenia and neutropenia continued until March, 1930. Since this date this patient's blood picture has been normal; the erythrocytes number 4,680,000; the hemoglobin is 14.36 Gm. (85.5 per cent). She looks well, and at the time of writing is perfectly well.

Comment.—This case started with all the characteristics of a fulminating case, the physical signs, symptoms and blood picture becoming grave over a four day period. Roentgen treatment was given on the fifth day; improvement was noted in the blood picture on the sixth day. On the fifteenth day from the date of onset the blood picture was normal and the patient felt well. The blood picture then remained fairly normal, even during confinement, for about three months. There was then a period of primary subchronic benign neutropenia lasting

over a period of about one year. The blood picture has remained normal during the past two and one-half years, which carries the reports to the time of writing.

CASE 2.—A white woman, aged 58, an American, married and the mother of two children, was taken ill on March 22, 1929, with sore throat, backache, one slight chill and nausea; she became progressively weaker. On March 23, I was called to her home to obtain a complete blood count. The blood study confirmed the suspected diagnosis of malignant neutropenia, and she was admitted to the hospital at noon of the same day. On admission her pulse rate was 115 and the temperature, 104 F. She looked acutely ill and pale and was nauseated; the throat was inflamed, and there was ulceration on one tonsil. Immediately on admission she was given a roentgen exposure of one-twentieth erythema dose, a 6 mm. aluminum filter being used at a distance of 50 cm. A smear taken from the throat

TABLE 2.—*Blood Count in Case 2* *

Date	Total White Cells	Myelo-blasts	Myelo-cytes	Juvenile Cells	Neutro-phils	Lympho-cytes	Endo-thelial Leuko-cytes	Türck's Cells	Unclas-sified Cells
3/23/29	750	1	..	3	7	88	..	..	1
3/23/29	Roentgen treatment								
3/24/29 a. m.	2,000	..	..	..	6	88	..	..	6
3/24/29 p. m.	900	..	..	1	7	91	..	..	1
3/25/29	Roentgen treatment								
3/25/29	575	..	2	3	4	86	2	1	2
3/26/29 a. m.	350	..	..	..	4	90	..	2	4
3/26/29	Transfusion								
3/26/29 p. m.	600	1	..	1	4	89	2	2	1
3/28/29	413	..	2	20	2	66	..	..	10
3/29/29	1,416	1	2	10	4	66	4	6	7
3/30/29	Transfusion								
3/30/29	2,325	..	..	19	23	40	..	11	7

* The cells that it was impossible to classify were thought to be degenerated neutrophils.

showed Vincent's organisms and staphylococci. The culture from the throat showed Staphylococcus aureus. The blood culture was positive, but was accidentally discarded by a technician before identification was completed. On March 25, another roentgen exposure was given. On March 26, the lesions of the mouth and throat were worse; there were dysphagia and vomiting, and the appetite was poor. The patient seemed weaker. Ten cubic centimeters of leukocytic extract and 10 cc. of whole blood were given subcutaneously in the back. On this date she was also given a transfusion, by the direct method, of 750 cc. of blood and 0.68 mg. of neoarsphenamine. Nausea, vomiting and dysphagia still continued through March 27 and 28. On March 29, she could not retain any food and was sleepy and difficult to arouse. She was given 2 cc. of boiled milk subcutaneously. The lesions of the mouth and throat had not responded to treatment. On March 30, she was given another transfusion of 700 cc. of blood. A few hours later her temperature rose to 105.6 F.; the pulse rate was 130. By evening of this day she had involuntary stools and voiding; the temperature dropped to 102.4 F.; she became cyanosed and comatose and died at 12:30 a. m. on March 31. The urine was negative at all times except for a trace of albumin. The erythrocytes numbered 4,500,000, and the hemoglobin, determined by the Newcomer method, was 12.17 Gm. (72 per cent).

Comment.—This was a typical case of primary fulminating malignant neutropenia in a woman, aged 58. Sore throat, backache, slight chill and nausea were the outstanding symptoms. She was sick for only two days when the first blood count showed a marked leukopenia and neutropenia, although she was said to have been in "poor health" for some years. This patient became progressively weaker and died nine days from the onset. Transfusions of blood and roentgen treatment failed to stimulate the granulopoietic tissue. On the last day there was an "agonal" discharge of the few remaining granulocytes.

CASE 3.—A white woman, aged 30, an American, married, who had no children but had had one miscarriage, was admitted to the hospital on June 19, 1930, suffering with a severe sore throat, headache, general malaise, membrane on the buccal mucous membrane, enlarged and tender anterior cervical lymph glands, a temperature of 103 F. and a pulse rate of 98. She had had a curettement for an incomplete abortion about four weeks previous to the present illness. One week following this operation sore throat with fever and slight nausea developed. (This may have been a first attack of neutropenia.) The symptoms abated in a few days, and she felt well again. On June 17, she was again taken ill, suffering with sore throat, headache and general malaise. The temperature at this time was 101 F., the pulse rate, 95, and there were marked stomatitis and pharyngitis. On June 18, the symptoms were more marked, with a slight enlargement of the anterior cervical lymph glands. A blood count at this time revealed a marked leukopenia and a total absence of granular cells. She entered the hospital on June 19 with a diagnosis of malignant neutropenia. Smears from the throat showed staphylococci, rare Vincent's organisms, fusiform bacilli and rare streptococci. Culture from the throat showed streptococci and staphylococci, Bacillus pyocyaneus predominating. The erythrocytes numbered 4,201,000, and the hemoglobin, determined by the Newcomer method, was 12 Gm. (71 per cent). The urine contained a slight trace of albumin and a few pus cells. (These pus cells may be explained by a few of the remaining neutrophils being eliminated onto the mucous membranes, a normal method for their destruction.)

The patient was given three roentgen exposures to the long bones, according to the method of Friedemann, on June 19, 20 and 21, but there was little evidence that it had stimulated the granulopoietic tissue. On June 20, it was felt that there had been a slight benefit due to the increase of granular cells from 10 per cent on the afternoon of June 19 to 28 per cent on the morning of June 20. However, the total count was lower, so that it was interpreted as a degenerative shift. Ten cubic centimeters of leukocytic extract and 5 cc. of sterile milk were administered on June 21, and 10 cc. of leukocytic extract on June 22 and 23. The physical signs and symptoms progressively grew worse, and the patient died on the morning of June 23.

Permission was given to examine the abdominal cavity and obtain a section of bone. The negative findings will be omitted. In the ilium five small ulcers were found having a crater diameter of 2 mm., with a hemorrhagic area surrounding them. Acute inflammatory reaction was absent. The appendix had been removed at a previous operation. The omentum was adherent to the ilium at various points on its anterior surface and was also adherent to the pelvic organs. The adhesions were old and fibrous. There was slight congestion of the mesenteric blood vessels. The liver was slightly enlarged and congested and microscopically showed only parenchymatous hypertrophy. The spleen was slightly darker than normal, with

moderate congestion; microscopically, there was moderate fine fibrosis. The kidneys showed moderate congestion; microscopically, there was a moderate amount of parenchymatous hypertrophy, with a moderate amount of hemorrhage into the interstitial substance. The uterus was normal in appearance, with atrophic endometrium, and was negative for necrosis or membrane formation. The fallopian tubes showed a marked congestion and marked chronic salpingitis. The right ovary was enlarged, 5 by 5 by 4 cm., and contained hemorrhagic and simple cysts. The left ovary had been removed at a previous operation. Grossly, the bone marrow of the tibia, rib and sternum was bright red and seemed to consist of red trabeculae and pale fluid fat. Microscopically, the hematopoietic tissue showed normoblasts, gigantoblasts and megakaryocytes. An occasional cell resembling a myeloblast was found, but they showed so much degeneration it was impossible to classify them definitely. A culture taken from the bone marrow showed a pure growth of Bacillus pyocyaneus.

TABLE 3.—*Blood Count in Case 3**

Date	Total White Cells	Myelocytes	Juvenile Cells	Neutrophils	Lymphocytes	Endothelial Leukocytes	Unclassified Cells
6/19/30 a. m.	650	..	3	..	95	2	..
	Roentgen treatment						
p. m.	888	2	8	..	84	2	..
6/20/30 a. m.	633	11	9	8	83	..	2
	Roentgen treatment						
p. m.	889	7	6	1	80	..	2
6/21/30 a. m.	500	..	1	..	86	2	8
	Roentgen treatment						
p. m.	553	..	6	..	84	..	4
6/22/30 a. m.	475	..	6	..	80	10	4
	Roentgen treatment						
p. m.	775	4	8	..	84	..	4
6/23/30 a. m.	3,180	..	2	..	92	2	4

* The unclassified cells were thought to be degenerated neutrophils.

Comment.—This is a typical case of primary fulminating malignant neutropenia in a patient who probably had had an attack of neutropenia one week following curettage. Just what bearing the curettage had on this case cannot be said, but during the illness there were no symptoms referable to the pelvic organs, and at autopsy there was no erosion or membrane formation in the vagina or the uterus. The agonal leukocytosis was due to an increase of lymphocytes, there being 2,925.6 lymphocytes in the last count.

CASE 4.—A white woman, aged 37, an American, married and the mother of one child, was taken ill on Feb. 7, 1931, with mild sore throat and acute gingivitis; her temperature rose to 101.1 F. For three months previous to this date she had complained of weakness on exertion, general lassitude, occasional sore throat and gums, slight neuritic pains in the right shoulder, headaches and a loss of 10 pounds (4.5 Kg.). As it was thought that these symptoms were possibly due to a mild secondary anemia (erythrocytes, 3,200,000; hemoglobin, 11.5 Gm. [68 per cent]), the patient had been taking liver extract (Valentine's), a compound of ferrous carbonate and ultraviolet ray treatments for the three months preceding the illness. The anemia improved—the hemoglobin was 14.02 Gm. (83 per cent) and the

erythrocytes numbered 4,070,000—but the symptoms continued. From February 1 to 7, the weakness was extreme. On February 6 the patient was unable to eat, and sleep was impossible, owing to the painful gums. On February 7, the patient was unable to leave her bed. The gums were extremely swollen and painful, and the submaxillary glands were swollen and tender. Other physical signs were negative except for a slight bronchitis and a moderately enlarged spleen. The pulse rate was 130, tumultus and irregular. The patient was drowsy and listless and complained of headache. The leukocyte and differential count disclosed a marked leukopenia and moderate neutropenia. Smears from the gums and throat showed streptococci. Cultures from the gums and throat gave a pure growth of streptococci. A dentist was called in consultation to treat the gums, and necrosis was found posteriorly in the region of the upper left incisor. The only other treatment given this patient was rest and a large amount of liquid diet rich in vitamin B, as follows: four egg yolks in milk (chocolate flavored), 750 cc.; tomato juice, 500 cc.; orange juice, 750 cc.; grape juice, 250 cc., and purée of pea soup, 250 cc. This amount was given daily, divided into five meals and administered every three hours. As soon as the patient was able to take more solid food, creamed asparagus and cooked oatmeal were added. (The patient gained 6 pounds [2.7 Kg.] on this diet during the two weeks in bed.)

The swelling of the gums was subsiding in twenty-four hours; the temperature was normal in three days, and there was gradual but steady improvement in the symptoms and the blood picture. At the end of seven days the gums were fairly well healed, and the blood picture was practically normal. Severe night sweats, involving the head, neck and chest, began at the end of the first week and continued until the end of the fourth week. Weakness persisted for four weeks, and the cardiac symptoms subsided as the weakness decreased. Other laboratory reports were as follows: The basal metabolism was minus 17; urinalyses showed a faint trace of albumin, rare hyaline casts and from 1 to 4 plus bacteria; concentration and dilution tests were normal; a phenolsulphonphthalein test gave a return of 50 per cent in two hours; the blood urea was 34 mg. per hundred cubic centimeters; the blood uric acid was 4.5 mg. per hundred cubic centimeters; the blood sugar was 105 mg. per hundred cubic centimeters; a serum bilirubin test showed less than 2 mg.; the Wassermann reaction was negative. The leukocyte and differential count did not maintain a normal level until March 24. The hemoglobin and erythrocytes always remained normal.

On August 6, there again was a leukopenia of 2,400, but the granular cells were 60 per cent. The only symptoms at this time were weakness and lassitude. (It might be noted here that although the percentage of granular cells was 60, there were only 1,440 total granular cells per cubic millimeter, whereas with a normal count there are about 4,080 per cubic millimeter. This demonstrated the necessity of taking the total granulocyte count into consideration in these cases.) On October 8, all of the signs and symptoms of appendicitis developed, with a fever and a leukocytosis of 11,900. Operation was refused. On October 12, the temperature, leukocytosis and symptoms had subsided. The blood picture then remained normal until December 18. The blood counts were then discontinued at the patient's request.

On Jan. 13, 1932, the symptoms of neutropenia again appeared, which the patient was then able to recognize. The neutropenia was more marked than during the first attack. The hemoglobin and erythrocytes were normal. On January 15, the patient was forced to go to bed because of lassitude, weakness and drowsiness, and she slept nearly forty-eight hours. There were no lesions of the mouth during this second attack, probably due to the rigid oral hygiene practiced in the interim.

TABLE 4.—*Blood Count in Case 4**

Date	Total White Cells	Eosinophils	Myelocytes	Juvenile Cells	Segmented Cells	Lymphocytes	Endothelial Leukocytes	Other Cells	Undifferentiated Cells
2/ 7/31	1,575	..	2	8	18	66	3	.....	3
2/ 7/31	1,266	..	8	11	27	49	1	.....	4
2/ 8/31	1,900	..	3	9	56	29	1	.....	2
2/ 9/31	2,250	..	4	3	35	52	5	.....	1
2/10/31	2,268	..	3	4	49	41	..	1 Türek	2
2/11/31	4,833	..	2	3	47	46	1	1 Türek	
2/13/31	3,375	..	..	2	65	30	2	1 Türek	
2/15/31	5,530	..	..	..	62	31	5	.....	2
2/18/31	4,650	1	..	..	69	26	3	.....	1
2/20/31	5,320	..	..	..	82	16	1	.....	1
2/23/31	4,050	..	1	..	70	25	3	.....	1
2/25/31	4,981	..	2	..	73	20	5		
2/27/31	5,690	..	..	..	71	23	4	.....	2
3/ 3/31	4,957	..	1	..	54	42	1	.....	2
3/ 4/31	5,140	..	..	..	71	25	3	.....	1
3/ 6/31	4,860	..	2	..	57	35	5	.....	1
3/10/31	6,000	..	..	4	64	27	5		
3/13/31	5,450	..	1	..	53	40	5	.....	1
3/17/31	3,410	..	2	..	60	31	5	1 Türek	1
3/18/31	4,430	..	..	..	61	31	6	.....	2
3/20/31	5,030	..	1	..	60	35	4		
3/24/31	5,800	..	2	..	64	28	5	.....	1
3/27/31	5,640	..	2	..	65	28	4	1 Türek	
3/31/31	6,475	..	1	..	70	24	5		
4/ 3/31	5,850	..	..	..	77	22	1		
4/ 8/31	5,100	..	..	1	65	33	1		
4/15/31	6,000	..	..	..	72	25	3		
4/23/31	6,150	2	2	..	60	34	2		
4/29/31	5,850	1	2	..	70	22	5		
5/11/31	6,100	..	..	..	67	31	2		
6/ 3/31	8,840	..	1	..	80	17	2		
6/16/31	4,522	..	1	..	66	33			
7/ 1/31	4,200	1	..	..	72	24	3		
7/17/31	5,450	..	..	..	83	16	1		
8/ 6/31	2,400	..	9	..	51	35	1	.....	4
8/ 7/31	3,530	..	9	..	61	30			
8/ 8/31	3,875	..	7	..	57	33	2	.....	1
8/10/31	3,850	..	2	..	67	31			
8/11/31	5,300	..	2	..	64	33	1		
8/13/31	5,740	..	1	..	62	35	2		
8/29/31	4,400	..	..	..	62	32	3	.....	3
10/ 9/31	9,325	2	1	..	70	27			
10/10/31	11,900	1	3	..	86	10			
10/12/31	6,800	1	..	..	71	27	1		
12/ 3/31	7,800	1	..	1	60	33	5	1 basophil	
1/13/32	1,945	..	..	..	14	78	7	1 basophil	
1/14/32	2,100	..	..	..	21	74	2	1 Türek	2
1/15/32	2,030	..	..	2	10	83	4	.....	1
1/16/32	1,600	2	..	3	18	71	5	1 basophil	
1/18/32	3,200	..	..	2	45	50	2	.....	1
1/19/32	3,900	..	..	..	58	40	1	.....	1
1/20/32	5,300	1	..	..	69	27	..	.....	1
1/21/32	5,270	..	..	..	72	28			
1/22/32	6,950	1	..	..	68	26	5		
1/25/32	5,625	2	..	..	64	31	2	1 basophil	
1/28/32	6,900	..	..	..	77	21	..	1 basophil	1
2/ 1/32	6,300	1	..	..	60	37	1	.....	1
2/ 5/32	8,800	..	..	..	74	25	1		
2/ 8/32	6,600	1	..	..	64	31	1	.....	1
2/11/32	3,900	3	..	..	58	34	4	.....	1
2/12/32	4,566	1	..	..	58	41			
2/15/32	4,950	3	1	..	56	37	2	.....	1
2/18/32	5,622	2	..	..	64	31	2	.....	1
2/24/32	6,400	2	..	..	63	34	1		
2/29/32	10,750	2	..	..	64	28	6	2 Türek	
3/ 1/32	8,925	2	..	..	71	21	3	1 basophil	
3/ 4/32	7,283	2	..	1	70	23	6		
3/10/32	6,500	2	..	..	63	33	1	.....	1
3/12/32	4,450	3	..	..	53	16	4	.....	2
3/14/32	4,200	1	..	..	64	33	1	.....	1
3/19/32	6,614	1	..	..	57	40	1	.....	1
3/29/32	8,220	2	..	..	78	19	1		
4/ 5/32	7,516	3	..	..	62	32	2	1 basophil	

* For purposes of brevity, the stab or rod nuclears have been included with the segmented forms. They were absent during the leukopenia, and there was never more than 7 per cent at any other time.

The cardiac symptoms were the same as in the first attack. The same treatment of rest and diet was instituted. In six days from the onset, the leukocytes rose to 5,300, with a normal neutrophilic granular percentage. At the end of a week, the night sweats again appeared, continuing for two weeks. Weakness lasted four weeks; the cardiac symptoms disappeared in four weeks. This patient had felt unusually well since the latter part of February, and was well at the time of writing.[95]

Comment.—This is apparently a typical primary subchronic recurring benign neutropenia. The patient did not give a history of any previous infection except gingivitis in 1925. A blood count was not made, so that neutropenia may have been present at that time. The patient stated that she had similar attacks in the early spring of 1929 and 1930, but thought it was influenza, and the blood was not examined. This patient did not enter the hospital, but was treated as an outpatient; she is still under observation.

SUMMARY OF CASES

These patients did not give a history of exposure to any of the physical or chemical agents known to produce benign or malignant neutropenia, nor did they give a history of any previous infection which might have had a bearing on the disease.

The clinical picture at the inception of the illness was the same for all four cases, case 4 having a more gradual onset.

These cases suggest that there is a fundamental difference in the pathologic changes underlying the recovered and the fatal cases. In the fatal cases, the maturation of granulocytes had ceased and the granulopoietic tissues were exhausted. A maturation factor for granulocytes has not yet been discovered so that a specific treatment could not be applied. In the recovered cases, maturation was arrested and the granulopoietic tissues were not exhausted, the fault seeming to be in the lack of a chemotactic factor to call the granulocytes to the circulating blood. In case 1, the roentgen ray in some unknown way stimulated this function to normal. Doan's [19] theory is that the roentgen ray brings about a destruction of some of the intact myeloid foci with a liberation of autogenous nucleotides, which then initiate the maturation and delivery of granulocytes from the remaining myeloid foci. In case 4, which was more mild, this function righted itself in time to prevent irreparable damage.

95. This case has been studied for another year (April 5, 1932, to May 1, 1933). The history was the same with a third attack of neutropenia in March, 1933. This case appears to present an annual cycle.

CHOLESTEROL AND LECITHIN PHOSPHORUS IN THE PLASMA OF ANEMIA OTHER THAN PERNICIOUS ANEMIA

INFLUENCE OF THERAPEUTIC MEASURES ON THESE CONSTITUENTS

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A disturbance of cholesterol and lecithin metabolism frequently accompanies anemia. The literature [1] reveals, however, a considerable variation in the results obtained by many observers, even when allowance is made for differences in technic. This variation may be partly due to deficient observations on the same patient and failure to correlate the various factors involved. In pernicious anemia there is a definite relationship between the stage of the disease and the lipoids of the blood.[2] Cholesterol and, in many instances, the plasma lecithin phosphorus are decreased during a relapse, but as remission is inaugurated there occurs a sudden rise in the lipoids of the blood, concomitant with the reticulocyte response. This reaction develops before there is significant alteration in the concentration of the red blood cells or hemoglobin, and is apparently proportional to the rate of remission.

In so-called secondary anemia, which is usually of the hypochromic type, the literature reveals only fragmentary and conflicting data.[1] Some investigators state that there does not seem to be any characteristic difference in the blood lipoids in different types of anemia.[3] This led certain observers to conclude that the degree of anemia is directly

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1. Muller, G. L.: The Cholesterol Metabolism in Health and in Anemia, Medicine **9**:119, 1930.

2. Muller, G. L.: The Relation of Cholesterol, Lecithin Phosphorus and Fatty Acids to the Remission of Pernicious Anemia, Am. J. M. Sc. **179**:316, 1930.

3. (*a*) Bloor, W. R., and MacPherson, D. J.: The Blood Lipoids in Anemia, J. Biol. Chem. **31**:79, 1917. (*b*) MacAdam, W., and Shiskin, C.: The Cholesterol Content of the Blood in Anaemia, and Its Relation to Splenic Function, Quart. J. Med. **16**:193, 1923.

related to the level of blood cholesterol.[4] Köhn [5] concluded that low values are found in all hypochromic anemias. Bloor [3a] considered the disturbance of the lipoid metabolism in anemias as a general reaction to the loss of cells and hemoglobin from the circulating blood, and he believed that low values of lecithin may be regarded as due to deficient assimilation of fat from the lack of sufficient corpuscles to bring about the change.[6]

It is obvious that knowledge concerning the blood cholesterol and lecithin phosphorus in so-called secondary anemias is fragmentary. Few data have been correlated with the stage and precise type of anemia, or with the state of the hematopoietic organs and alterations induced by therapy. We have studied sixty-one cases of various types of anemia other than pernicious anemia from these points of view (table 1).

TABLE 1.—*Classification of Cases*

	Number of Cases
Anemia due to chronic loss of blood	10
Anemia due to acute loss of blood	10
Idiopathic hypochromic anemia with and without the association of faulty diet	15
Carcinoma	6
Myelogenous leukemia	6
Idiopathic aplastic anemia	3
Splenic anemia	3
Pulmonary tuberculosis	1
Nontropical sprue	1
Osteomalacia	1
Osteosclerotic anemia	1
Hodgkin's disease	1
Tuberculous adenitis	1
Myxedema	1
Myeloma and plasma cell leukemia	1
Total	61

PROCEDURE AND METHODS

Determinations of plasma cholesterol and lecithin phosphorus were made by methods employed previously.[7] In thirteen of the sixty-one cases only one determination was made, but the remainder were studied repeatedly for weeks or months.

4. (*a*) Schnabel, T. G.: Blood Cholesterol in Gastro-Enterologic Cases, Am. J. M. Sc. **160**:423, 1920. (*b*) Strathmann-Herweg, H.: Untersuchungen über den Cholesteringehalt des Blutserums, Monatschr. f. Kinderh. **19**:20, 1920. (*c*) Dönomae, I.: Ueber das Blutlipoid bei Ankylostomiasisanämien, nebst einem Anhang über den Blutzucker, das Serumeiweiss und die Senkungsgeschwindigkeit der roten Blutzellen, Jap. J. M. Sc. Tr. **1**:385, 1927.

5. Köhn, H.: Ueber den Cholesterinspiegel im Serum bei der perniziösen Anämie, Deutsches Arch. f. klin. Med. **148**:357, 1925.

6. Bloor, W. R.: The Distribution of the Lipoids ("Fat") in Human Blood, J. Biol. Chem. **25**:577, 1916.

7. Muller, G. L., and Talbott, J. H.: The Effect of High Altitudes on the Cholesterol, Lecithin and Fatty Acids in the Plasma of Healthy Men, Arch. Int. Med. **47**:855 (June) 1931.

RELATION OF CHOLESTEROL AND LECITHIN PHOSPHORUS TO RED BLOOD CELL AND HEMOGLOBIN CONCENTRATION

Before discussing the types of anemia, we shall consider the relation of anemia per se to the plasma cholesterol and lecithin phosphorus.

In chart 1 *A*, three hundred and fifteen determinations of cholesterol have been plotted against the numbers of the red blood cells per cubic

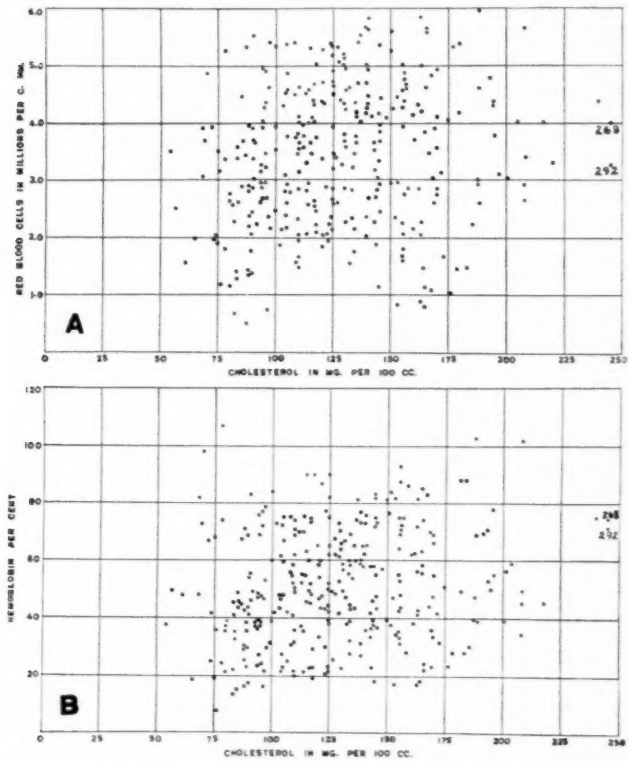

Chart 1.—Cholesterol in secondary anemia. The amount of cholesterol in the blood plasma of sixty-one patients with anemia other than pernicious anemia plotted against (*A*) the number of red blood cells and (*B*) the concentration of hemoglobin.

millimeter in the peripheral blood. The values of cholesterol range from 54 to 292 mg. per hundred cubic centimeters of plasma, and the red blood cells vary from 500,000 to 5,900,000 per cubic millimeter; but low values of cholesterol were found when the red blood cells were over 5,000,000, as well as when they were below 1,000,000 per cubic millimeter. Conversely, high normal values of cholesterol were frequently found when the red blood cells were few.

In chart 1 *B* the level of plasma cholesterol is plotted against the percentage of hemoglobin. These charts, as well as the data for pernicious anemia,[2] indicate that no general statement can be made as to the relation between the concentration of red blood cells or hemoglobin and the concentration of plasma cholesterol in anemia. The same con-

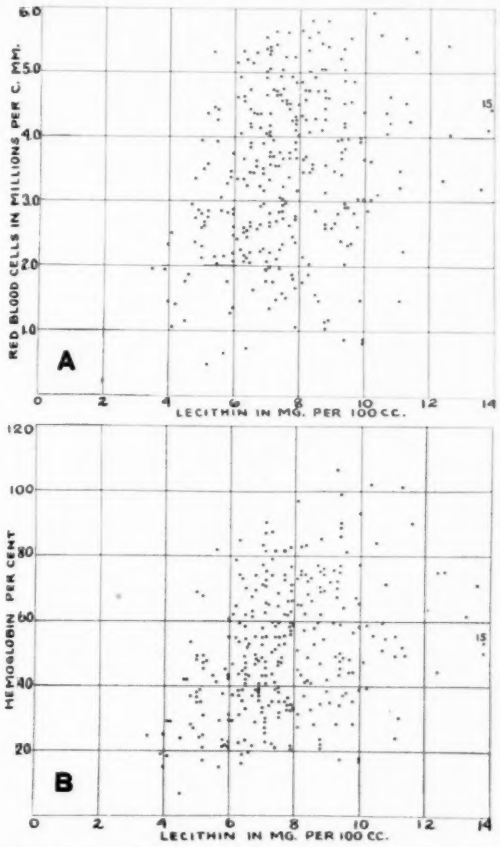

Chart 2.—The relation of the plasma content of lecithin phosphorus at various stages of anemia other than pernicious anemia to (*A*) the number of red blood cells and (*B*) the concentration of hemoglobin.

clusion can be drawn with regard to the lecithin phosphorus (chart 2). Whatever may be the underlying cause of disturbed lipoid metabolism, anemia per se is not directly related to the level of the cholesterol and lecithin phosphorus in the blood.

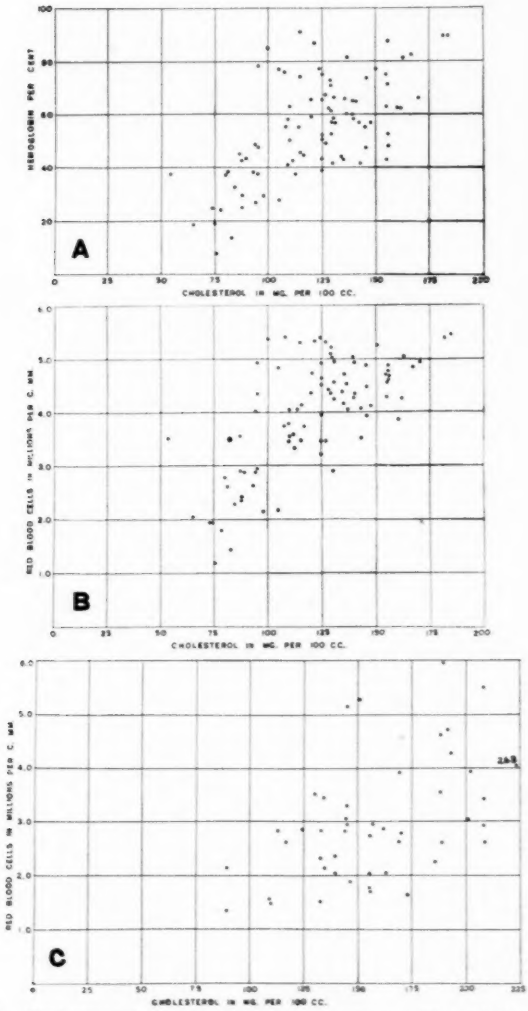
HEMOGLOBIN PER CENT
A
CHOLESTEROL IN MG. PER 100 CC.
RED BLOOD CELLS IN MILLIONS PER C. MM.
B
CHOLESTEROL IN MG. PER 100 CC.
RED BLOOD CELLS IN MILLIONS PER C. MM.
C
CHOLESTEROL IN MG. PER 100 CC.

Chart 3.—Cholesterol in anemia due to hemorrhage. The relation of plasma cholesterol (*A*) to the hemoglobin, and (*B*) to the red blood cells in ten cases of anemia caused by chronic loss of blood, and (*C*) to the red blood cells in ten cases of anemia caused wholly or in part by acute hemorrhage. Note the normal or high values in comparatively severe cases of anemia due to acute loss of blood. The lowest values recorded occurred in three cases in which chronic slight loss of blood had occurred.

Although there is no correlation between the degree of anemia and the levels of the lipoids, these levels sometimes in certain types of anemia besides pernicious anemia manifest certain definite characteristics.

LIPOIDS IN ANEMIA DUE TO CHRONIC LOSS OF BLOOD

The relationships of cholesterol to hemoglobin and to red blood cells in the ten cases of anemia due to chronic loss of blood are illustrated in chart 3. The data for lecithin phosphorus plotted in the same manner show exactly the same relationships (chart 5 *A*). It is evident that in anemia due to chronic loss of blood both cholesterol and lecithin phosphorus tend to be low when the anemia is severe, which is more evident when the concentration of hemoglobin, rather than the level

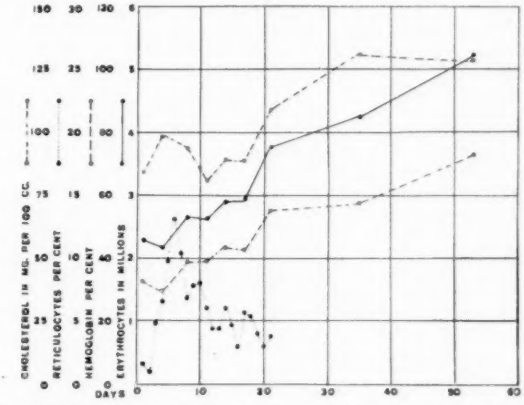

Chart 4.—Cholesterol, red blood cells, hemoglobin and reticulocytes in a patient with anemia due to a chronic loss of blood. Iron and ammonium citrate were given in large doses. The cholesterol began to increase when the reticulocyte response subsided, or about three weeks after iron therapy was begun.

of red blood cells, is considered. With improvement which in the absence of complications was readily brought about by adequate doses of iron, both the lecithin phosphorus and the cholesterol rose gradually to within normal limits.

In four of these cases there occurred a marked reticulocyte response to iron therapy. In the other six, in which there was less anemia, the reticulocyte reaction was relatively slight. The relation of the reticulocyte response to the cholesterol level in one case is illustrated in chart 4. On comparing the reticulocyte reaction in these patients with that in patients with pernicious anemia treated with liver or other potent material,[2] there is discernible a marked and possibly significant difference. In pernicious anemia the rise of cholesterol, and in many instances,

of lecithin phosphorus, is concomitant with the increase of reticulocytes, while in anemia associated with chronic loss of blood, the cholesterol remains low during the increase of reticulocytes, but as the reticulocytes decrease the lipoids become augmented. In anemia of this type, as is illustrated in chart 4, the rise of the concentration of red blood cells and hemoglobin is considerable before cholesterol and lecithin phosphorus are increased.

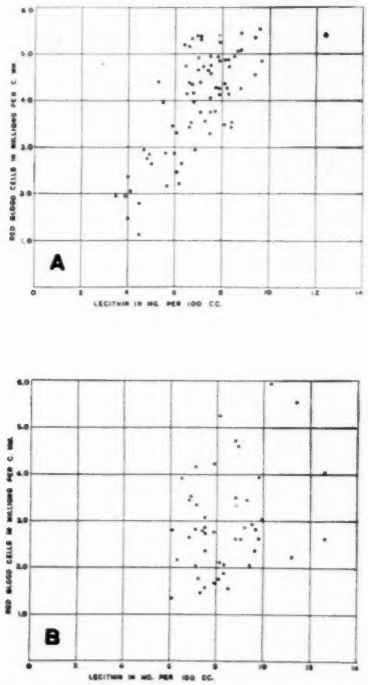

Chart 5.—Lecithin phosphorus in anemia due to hemorrhage, plotted against the red blood cells in (*A*) ten cases caused by chronic loss of blood and (*B*) ten cases caused wholly or in part by acute hemorrhage.

Intercurrent infection developed in two of the ten cases and caused fever. This was accompanied by a moderate fall of cholesterol and lecithin phosphorus from the previous level.

LIPOIDS IN ANEMIA DUE TO ACUTE LOSS OF BLOOD

No previous loss of blood had occurred in five of the ten patients with anemia especially due to acute loss of blood. In at least three there had been recurrent slight loss of blood from the gastro-intestinal

tract before the sudden loss of blood that particularly induced anemia. Thus, the reserve supplies of blood-building material in the latter patients were diminished, so that they may be considered intermediate in type between those with no previous loss of blood and the ten with chronic loss of blood of considerable degree. In most instances the observations were not made immediately after the hemorrhage.

The relation of cholesterol and lecithin phosphorus to the red blood cells is illustrated in charts 3 *C* and 5 *B*, respectively. Similar charts were obtained from plotting data for the lipoids against the percentage of hemoglobin, as the color index was usually close to unity. Contrasting *C* with *A* and *B* in chart 3 and *A* with *B* in chart 5, it is evident that the behavior of the lipoids differs in anemia due to chronic loss of blood and that due to acute loss of blood. In the five uncomplicated cases of anemia due solely to acute hemorrhage, the lipoids were within the normal range, but the degree of anemia was as great as in the cases due to chronic loss of blood, in which the cholesterol and the lecithin phosphorus were below normal.

The few subnormal values of cholesterol obtained in the cases in which acute loss of blood was particularly responsible for the anemia (chart 3 *C*) occurred in three cases in which there had been bleeding previously. Transient infection accounted for decreased plasma lipoids in two observations.

Reticulocyte responses to the acute loss of blood occurred in all ten cases. The relation of the plasma lipoids to the reticulocyte response in the cases differed from that seen in cases caused by chronic loss of blood. As a rule, the outpouring of reticulocytes following the acute hemorrhage was accompanied by hypercholesterolemia and lecithinemia. In three patients in whom the acute hemorrhage was superimposed on chronic loss of blood the plasma lipoids were decreased and the lowest values were concomitant with the peak of the reticulocyte response. The results in these three cases simulated those in cases of anemia due to chronic loss of blood, which is not surprising because the patients had had a slight chronic loss of blood formerly. This recurrent slight drain on the formation of blood thus appears to have affected the cholesterol in the direction that it takes after repeated and pronounced chronic loss of blood.

LIPOIDS IN IDIOPATHIC HYPOCHROMIC ANEMIA WITH AND WITHOUT ASSOCIATION OF FAULTY DIET

Of the fifteen patients with this chronic condition, nine had achlorhydria and the rest hypochlorhydria. Determinations were made of the lipoids, red blood cells and hemoglobin at least weekly, and the reticulocytes were counted daily during the early days of iron therapy. Eleven

cases were studied for periods varying from five to eighteen weeks, while the four remaining cases were observed for shorter intervals.

The surprising fact is that in this group there is no positive and consistent relationship between the cholesterol or the lecithin phosphorus and the concentration of hemoglobin or red blood cells, color index or reticulocyte response to iron. Data for six cases of hypochromic anemia with achlorhydria are given in table 2. It is evident that neither in pernicious anemia (hyperchromic) nor in idiopathic hypochromic anemia are the levels of blood lipoids related to achlorhydria.

In seven of fifteen patients with varying degrees of anemia the plasma cholesterol and lecithin phosphorus were within a narrow normal range throughout. In the remaining cases, except two, the lipoids varied considerably at a level that was subnormal or near the lower

TABLE 2.—*Red Blood Cells, Hemoglobin, Cholesterol and Lecithin Phosphorus in Idiopathic Hypochromic Anemia with Achlorhydria*

Patient	Sex	Age	Time of Observations in Weeks	Red Blood Cells, Millions per C.Mm.		Hemoglobin, per Cent		Cholesterol, Mg. per 100 Cc. of Plasma		Lecithin Phosphorus, Mg. per 100 Cc. of Plasma	
				Low	High	Low	High	Low	High	Low	High
1	♀	47	13	3.4	5.3	41	85	94	131	6.2	8.0
2	♀	44	18	4.2	5.5	47	83	87	125	5.3	8.2
3	♀	32	15	3.9	5.4	39	74	85	150	5.0	8.9
4	♀	33	9	4.4	5.5	62	74	140	166	8.3	8.8
5	♀	42	10	2.1	4.6	28	85	156	165	7.9	9.4
6	♀	25	12	5.0	5.8	55	83	139	155	7.9	8.4

limit of normal. The values recorded, however, showed no definite trend, but were frequently highest at a time when the anemia was most severe.

In two patients the anemia was severe, with 1,300,000, and 2,200,000 red blood cells per cubic millimeter and 16 and 22 per cent hemoglobin, respectively. In both cases the cholesterol and lecithin phosphorus were somewhat low at the height of the anemia. In each case there was a rise of both cholesterol and lecithin phosphorus before the reticulocyte response to iron had subsided, comparable to what occurs in pernicious anemia (chart 6).

LIPOIDS IN ANEMIA ASSOCIATED WITH CARCINOMA OF THE STOMACH

In five of the six cases of carcinoma of the stomach the hypochromic anemia could be attributed, at least in part, to chronic loss of blood, and in only one was there a significant decrease of anemia. In all of the cases the cholesterol values were below 125 mg. per hundred cubic centimeters (chart 7), and the lecithin phosphorus was below 7 mg. per hundred cubic centimeters regardless of the level of red blood cells, hemoglobin and reticulocytes, except in the case in which the anemia

definitely decreased as the result of iron therapy. Data concerning this patient are given in chart 8. No history or evidence of bleeding could be obtained. This patient had confined himself to a milk diet for many months.

LIPOIDS IN CHRONIC MYELOGENOUS LEUKEMIA AND CHLOROMA

Five cases of chronic myelogenous leukemia and one case of chloroma were studied. All of the patients were treated with arsenic by Dr. Claude E. Forkner, and he furnished the figures of the blood counts and the determinations of hemoglobin.

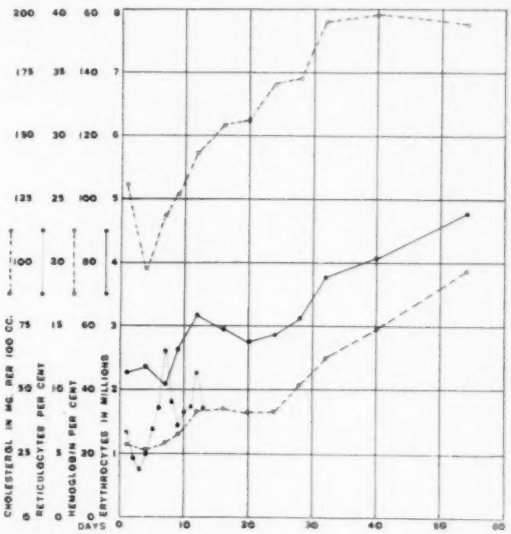

Chart 6.—Cholesterol in idiopathic hypochromic anemia with or without the association of a faulty diet. The relation of cholesterol to the reticulocyte response, red blood cells and hemoglobin. During the first month of observation, this patient had a slight fever (about 100 F. daily). The curve for the cholesterol is similar to the one obtained in cases of pernicious anemia after liver therapy.

The relationship between the red blood cell level and that of cholesterol is illustrated in chart 9 *A*. The striking fact is brought out that in chronic myelogenous leukemia there is a tendency toward subnormal values of cholesterol, irrespective of whether or not there is anemia. Rarely was the value of cholesterol near the normal average. The lecithin phosphorus, on the other hand, did not show a value below normal (chart 9 *B*). Thus there is a definite dissociation between cholesterol and lecithin phosphorus in chronic myelogenous leukemia in contrast to the association found in various types of anemia.

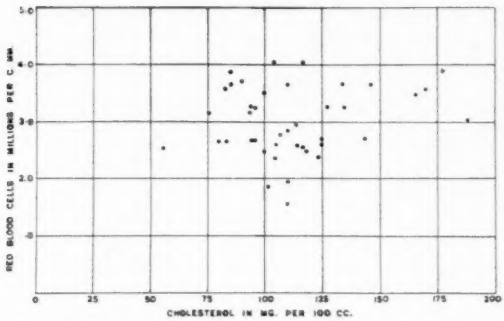

Chart 7.—Cholesterol in six cases of carcinoma of the stomach with anemia. Antianemic treatment influenced the red blood cells, hemoglobin and cholesterol but little, except in one case.

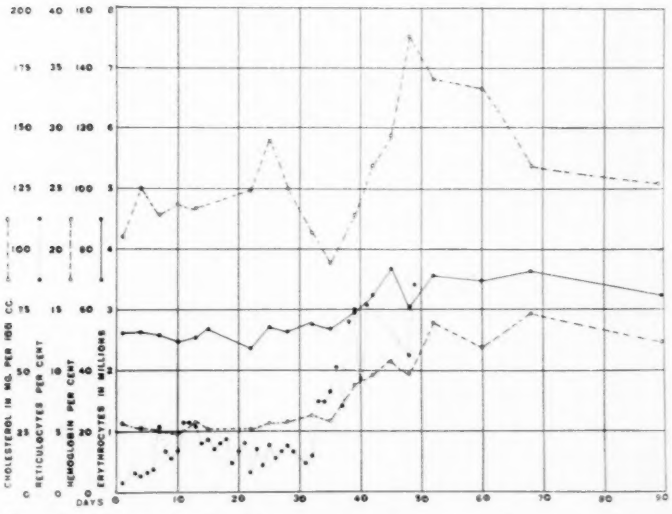

Chart 8.—The relation of cholesterol to the reticulocyte response, red blood cells and hemoglobin in one case of carcinoma of the stomach in which there was temporary improvement. Liver therapy for the first twenty-two days caused no improvement. Beginning on the thirtieth day, 6 Gm. of iron and ammonium citrate was administered daily. The patient responded with a marked increase of reticulocytes.

There was no positive correlation between the level of the plasma cholesterol and the basal metabolic rate or the number or type of white blood cells in the peripheral blood.

In the case of chloroma the anemia was severe, and both the lecithin phosphorus and the cholesterol were subnormal. The patient was observed only during the last two weeks of life, when he had a temperature varying daily from 99.5 to 104 F.

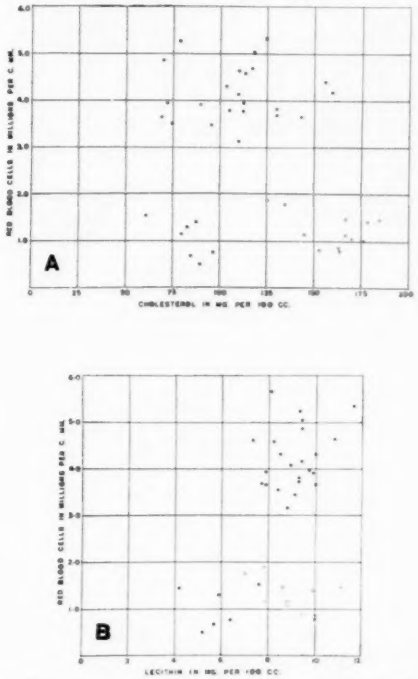

Chart 9.—*A*, cholesterol plotted against the red blood cells in myelogenous leukemia (●) and aplastic anemia (○). *B*, the relation of lecithin phosphorus to the red blood cells in myelogenous leukemia (●) and aplastic anemia (○). Note the dissociation of the levels of cholesterol and lecithin phosphorus in cases of myelogenous leukemia and the normal high values of cholesterol and lecithin phosphorus in cases of advanced aplastic anemia.

LIPOIDS IN APLASTIC ANEMIA

The findings in three cases of aplastic anemia were in sharp contrast to those in cases of chronic myelogenous leukemia. The differences are shown in chart 9, in which determinations of cholesterol and lecithin phosphorus have been plotted against the number of red blood cells for

the cases of aplastic anemia and of myelogenous leukemia. In spite of the severity of the anemia in the cases of aplastic anemia, both the cholesterol and the lecithin phosphorus, except as will be noted, remained within the upper limits of normal, in contrast to the lower levels in myelogenous leukemia, irrespective of anemia. In the cases of aplastic anemia yielding the lower figures for cholesterol the samples of blood were taken during fever induced by protein shock therapy or a transfusion of blood.

LIPOIDS IN MISCELLANEOUS TYPES OF ANEMIA

This group includes anemias of various origin. Facts about the eleven cases are given in table 3.

Of the three patients with splenic anemia, two had subnormal cholesterol and lecithin phosphorus, while in the third these constituents

TABLE 3.—*Red Blood Cells, Hemoglobin, Cholesterol and Lecithin Phosphorus in Miscellaneous Anemias*

Diagnosis	Sex	Age	Number of Determinations	Cholesterol, Mg. per Cc.	Lecithin Phosphorus, Mg. per Cc.	Red Blood Cells, Millions per C.Mm.	Hemoglobin, per Cent
Splenic anemia	♂	24	1	90	4.8	3.4	54
Splenic anemia	♂	65	1	117	6.0	4.2	90
Splenic anemia	♂	7	1	143	6.9	2.3	36
Pulmonary tuberculosis	♀	20	2	83-89	5.0-5.8	2.8-3.4	38-40
Nontropical sprue	♂	50	2	68-78	5.6-6.3	3.0-3.4	74-82
Osteomalacia	♀	38	1	88	...	3.9	71
Osteosclerotic anemia	♂	45	3	89-114	5.0-7.0	2.0-2.1	32-41
Hodgkin's disease	♂	48	1	91	7.4	3.0	55
Tuberculous adenitis	♀	52	1	121	10.7	4.3	60
Myxedema	♀	42	2	197-292	10.4-13.6	2.9-3.1	55
Myeloma with plasma cell anemia	♀	38	1	163	7.4	2.3	41

were normal. In the latter case there had been a hemorrhage one week previously. Fever in the patient with pulmonary tuberculosis may have influenced the lipoids regardless of the anemia and the disease process. In the case of tuberculous adenitis without fever the lipoid levels were normal.

Comments regarding the other cases are not necessary except as follows.

In the patient with myxedema with mild anemia, both cholesterol and lecithin phosphorus were above normal. With thyroid extract therapy the cholesterol decreased from 292 to 197 mg. per hundred cubic centimeters, and the lecithin phosphorus, from 13.6 to 10.4 mg. per hundred cubic centimeters in eight days.

COMMENT AND CONCLUSIONS

The lipoid level in the blood plasma certainly does not bear any direct relation to the concentration of red blood cells or of hemoglobin.

Low values of cholesterol and lecithin phosphorus are not always found in severe hypochromic anemia, as has been claimed.[8] However, by frequent examination of the blood in the same patient and by analyzing the anemias of various types and causes, certain definite characteristics have been made out regarding the trends of the blood lipoids.

It has been pointed out that the lipoids behave differently in anemia due to chronic loss of blood and to that due to acute loss of blood, and that their increase following iron therapy in anemia caused by chronic loss of blood commences after the reticulocyte response, in contrast to an approximate paralleling of the reticulocyte reaction to liver therapy in pernicious anemia.

The observations permit the scanty data in the literature [4c] on the lipoids in anemia due to chronic loss of blood to be brought into line.

The normal range of lipoids with a tendency to hypercholesteremia and hyperlecithinemia in anemia due to acute loss of blood is of interest in connection with the observations of Feigl [8] immediately after acute hemorrhage and for a short period subsequently. He found a uniform increase of cholesterol in the blood under such circumstances, which was evident on the first day and marked forty-eight hours after the acute loss of blood. He noted that the hypercholesteremia persisted in a diminishing degree for more than a week. The rise was less marked in undernourished persons. Unfortunately, his report gives no data to indicate the severity of the anemia.

The cause of lipoidemia after acute hemorrhage in man and in animals [1] has been variously interpreted. It is evident that it is not altogether due to a lack of red blood cells and decreased oxidation, as has been claimed by some investigators,[9] since an even greater lack of red blood cells is present in many anemias that show subnormal values of the blood lipoids. In acute hemorrhage there may be, however, a sudden decrease of lipase and a decrease of the metabolism of lipoids, as has been suggested by Horiuchi [10] and Sakai.[11] Bloor [12] considered that there was an outflow of lipoids into the blood in a greater quantity than the normal mechanism could dispose of at once, and in this outflow the displacement of fat by the blood-forming tissue may play an important part.

8. Feigl, J.: Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden im Blute nach Blutentziehung, Biochem. Ztschr. **115**:63, 1921.

9. Boggs, T. R., and Morris, R. S.: Experimental Lipemia in Rabbits, J. Exper. Med. **2**:553, 1909.

10. Horiuchi, Y.: Studies on Blood Fat: II. Lipemia in Acute Anemia, J. Biol. Chem. **44**:363, 1920.

11. Sakai, S.: Zur Pathogenese der Lipämie, Biochem. Ztschr. **62**:387, 1914.

12. Bloor, W. R.: Lipemia, J. Biol. Chem. **49**:201, 1921.

Fishberg and Fishberg [13] have offered another explanation of the mechanism of the lipoidemia. They found that after a sudden loss of blood the total proteins were decreased, and that there was a shift in the albumin-globulin ratio in favor of the latter. They thought, therefore, that the increase of the lipoids after hemorrhage was due to the loss of serum proteins, and that the lipoidemia might be considered as a compensatory phenomenon, for the purpose of maintaining the colloidal osmotic pressure in the blood at a normal level. As confirmatory evidence of the foregoing hypothesis, Fishberg [14] showed that the osmotic pressure in lipemic blood is higher than in blood diluted to the same concentration of protein, and that this difference becomes apparent at the same time as the lipoids in the blood start to rise.

The reason for the low plasma cholesterol and lecithin in anemia caused by chronic loss of blood is not clear. Possibly there is merely a gradual depletion of the lipoids because of the constant loss of these substances from the body at a rate faster than they can be provided by the intake or the synthesis of food. On the other hand, it has been repeatedly shown [1] that low values of cholesterol may be obtained by increasing the functional activity of the reticulo-endothelial system, the main functioning part of the hematopoietic organs. During relapse in pernicious anemia it is highly probable that there is an increase in function of this system, and that this abnormal activity decreases as remission ensues. The relapse is accompanied by subnormal values of the lipoids, which increase promptly as remission begins. In anemia caused by chronic loss of blood the activity of the bone marrow is increased, as shown by the hyperplasia of the red blood cells. To account for the delayed rise of lipoids as compared with that in pernicious anemia, one must assume that an abnormal activity of the reticulo-endothelial system persists until the reticulocyte response to iron has subsided, since the lipoids do not increase until then. Whether or not such a correlation exists in anemia caused by chronic loss of blood can be determined only after material from the bone marrow, obtained by biopsy, has been studied at various stages. In anemia due to acute loss of blood there is also an increased activity of the hematopoietic organs with a rapid replacement of the fat in the bone marrow by cellular tissue. The possible relation of the lipoids to the activity of the hematopoietic organs may be obscured, however, as the cholesterol is mobilized in an effort to overcome the lowering of osmotic pressure caused by the sudden loss of plasma proteins.

13. Fishberg, E. H., and Fishberg, A. M.: The Mechanism of the Lipemia of Bleeding, Proc. Soc. Exper. Biol. & Med. **25**:296, 1928; Biochem. Ztschr. **195**:20, 1928.

14. Fishberg, E. H.: Relations of the Serum Proteins and Lipoids to the Osmotic Pressure, J. Biol. Chem. **81**:205, 1929.

That there may be a possible relation of cholesterol to cell proliferation in the bone marrow is also suggested by the low cholesterol values we and other investigators [1] have found in chronic myelogenous leukemia. Kipp [15] observed that hypocholesteremia occurs also in acute infectious diseases like pneumonia, a disease in which there is a considerable production of white blood cells. He found that variation of cholesterol in the serum depended on the activity of the leukocytes.

The significance of the dissociation between cholesterol and lecithin phosphorus in chronic myelogenous leukemia is not clear. It has been assumed that lecithin phosphorus may possibly participate in the active formation of red blood cells, Sundstroem and Bloor [16] reported that in animals subjected to low barometric pressure there was a decrease of the lipoid phosphorus in the blood. This they suggested might be due to an enrichment of the erythropoietic organs with lipoid material, as the first phase of stimulation resulting from low barometric pressure. Whether lecithin phosphorus in the blood plasma is influenced by the proliferation of white blood cells is not known. The foregoing findings certainly suggest, however, that there is a definite dissociation between the two mechanisms controlling the level of cholesterol and lecithin in the blood stream. It appears as though the lecithin phosphorus in the plasma is not influenced by hyperplasia of the cells of the myelogenous series.

Two cases reported in the literature [17] with single determinations of the blood lipoids corroborate our findings that in spite of severe anemia these elements may remain normal with a tendency to high figures in aplastic anemia, a condition in which the activity of the bone marrow is reduced to a minimum.

Considerable difference of opinion [18] has been expressed as to the relation of the cholesterol and lecithin level in the plasma and carcinoma. In the later stages of this disease there is a tendency for the lipoids to be lower than normal. In an analysis of fifteen cases of anemia associated with carcinoma recorded in the literature,[1] it was found that six patients had subnormal cholesterol values, and of these, all but one, in

15. Kipp, H. A.: Variation in the Cholesterol Content of the Serum in Pneumonia, J. Biol. Chem. **44**:215, 1920.

16. Sundstroem, E. S., and Bloor, W. R.: The Physiological Effects of Short Exposures to Low Pressure, J. Biol. Chem. **45**:153, 1920.

17. Gibson, R. B., and Howard, C. P.: Metabolic Studies in Pernicious Anemia, Arch. Int. Med. **32**:1 (July) 1923. Antonelli, G.: Colesterinemia e resistenza globulare negli stati anemici, Policlinico (sez. med.) **21**:341, 1914.

18. Mattick, W. L., and Buchwald, K. W.: Blood Cholesterol Studies in Cancer: IV. Other Lipoid Partition, J. Cancer Research **13**:157, 1929. Klein, W., and Dinkin, L.: Beiträge zur Kenntnis der Lipoide des menschlichen Serums und zur Methodik der Lipoidbestimmung, Ztschr. f. physiol. Chem. **92**:302, 1914. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, Arch. Int. Med. **20**:599 (Oct.) 1917.

whom the location of the tumor was not stated, had carcinoma of the esophagus or the stomach. Our six patients with carcinoma of the stomach all had subnormal values. When the anemia can be lessened, the lipoids may increase, as in anemia caused by chronic loss of blood, as was shown in one of our cases.

In idiopathic hypochromic anemia and anemia associated with certain chronic dietary defects the distinguishing feature with regard to the level of the blood lipoids seems to be the lack of consistency. This may, however, be more apparent than real, and with further knowledge of the mechanisms of this sort of anemia, the lack of consistency may be explained. Patients, besides being treated with iron, were given an adequate diet, and although the anemia improved markedly, in most instances the lipoids remained uninfluenced. This indicates that the intake of food plays a subordinate rôle in whatever may be the mechanism that regulates the lipoids in the plasma. Histologically, the hematopoietic organs in these anemias show erythroblastic and normoblastic hyperplasia.[19]

Certain suggestive observations may be recorded. Thus protein shock and rise in temperature, conditions which can affect the reticulo-endothelial system, tended to lower the level of cholesterol and lecithin phosphorus in the blood. Hypothyroidism in the one case that we studied overshadowed any tendency toward hypocholesteremia that may exist in anemia. It is clearly evident [1] that conditions other than those recognized as affecting the hematopoietic organs, such as diabetes, nephritis or thyroid activity, may be associated with a disturbance of the level of cholesterol and lecithin in the blood plasma, but it is probable that there is a common mechanism. One may conclude, however, from the study of the cholesterol and lecithin phosphorus of the blood plasma in anemia that there seems to be some support for the hypothesis that the functional activity of the reticulo-endothelial system is intimately associated with controlling the level of the lipoids in the blood. The apparently contradictory results obtained in certain anemias may be explained satisfactorily with the elucidation of the exact functional state of the hematopoietic organs.

SUMMARY

The behavior of plasma cholesterol and lecithin phosphorus in sixty-one cases of anemia other than pernicious anemia has been determined and correlated with various factors.

19. Weiner, W., and Kaznelson, P.: Ueber die zellige Zusammensetzung des Knochenmarkes nach Erfahrungen mittels der Sternalpunktion nach Seyfarth, Folia haemat. **32**:233, 1926. Dameshek, W.: Primary Hypochromic Anemia (Erythro-Normoblastic Anemia): A New Type of Idiopathic Anemia, Am. J. M. Sc. **182**:520, 1931.

The plasma lipoids were not related to anemia per se, as has been claimed, but definite characteristics were obtained in certain disorders of the blood. In anemia due to acute loss of blood the lipoids remained at normal levels or were high, while in that caused by chronic loss of blood they tended to be low at the height of the anemia, but increased with improvement after the reticulocyte response had subsided. This is in contrast to their behavior in pernicious anemia, in which the increase of the lipoids parallels the reticulocyte response.

In idiopathic hypochromic anemia with or without the association of a faulty diet, the chief characteristic of the course taken by the lipoids was the lack of consistency. In carcinoma of the stomach associated with anemia, the lipoids remained low except when the anemia decreased.

In chronic myelogenous leukemia, a dissociation between plasma cholesterol and lecithin phosphorus occurred. The level of cholesterol was found to be subnormal, or at the lower limit of normal, even when no anemia was present, while the lecithin phosphorus was normal. In aplastic anemia, on the other hand, the lipoids were high in spite of severe anemia.

EFFECT ON THE REFLEXES OF THE CAROTID SINUS OF RAISING THE INTRACRANIAL PRESSURE

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MINNEAPOLIS

The work of Cushing [1] on intracranial pressure, published in 1902, brought out an important mechanism of adjustment in the body. He found experimentally that as intracranial pressure was gradually raised toward the level of the blood pressure, the blood pressure rose enough to keep ahead of it and to keep the brain sufficiently supplied with blood so that respiration continued. On the other hand, when intracranial pressure was raised suddenly, respiration would cease temporarily, following which the blood pressure would quite rapidly climb above the pressure of the cerebrospinal fluid, and respiration would begin again. Vagus effects, shown by slowing or stopping of the heart, were observed unless the intracranial pressure was increased very gradually and slowly. Meanwhile, by means of a window in the cranium of the dog, the pial vessels and the superior longitudinal sinus were observed. As the intracranial pressure was raised, increasing evidence of stasis and anemia was seen. As the pressure increased, the longitudinal sinus wavered, narrowed and thinned until it completely collapsed. At the equalization of pressures a marked blanching of the brain occurred. The blue veins in the sulci remained filled with blood. The arteries became very narrow; there was very little if any circulation between them. The centers were therefore poorly, if at all, supplied with blood. At this point death of the animal did not occur, as had been previously supposed, but the blood pressure rose sufficiently to overcome the high intracranial tension. The gyri became rosy again. Centers were once more nourished, and respiration, if it had ceased, began again. Thus circulation through the brain was reestablished. Cushing therefore concluded that the increase of the blood pressure was due to an anemia of the vasomotor area, just as the cessation of respiration was due to an anemia of the respiratory center when the cerebrospinal fluid pres-

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1. Cushing, H.: Am. J. M. Sc. **124**:375, 1902.

sure was too high. This work was confirmed by Eyster, Burrows and Essick.[2]

Since these experiments were performed, the influence of the carotid sinus has been discovered, and a considerable amount of work has been done on it. Since the work of Hering [3] and Heymans,[4] the "depressor" action of the sinus has been willingly conceded, but concerning its "pressor" action which results from an increase of blood pressure in the sinus there is some doubt. Some investigators, among whom are Danielopolu and co-workers,[5] Tomanek [6] and Schroeder,[7] held, and with apparently good evidence, that at least in higher mammals a pressor reflex can be elicited by direct pressure on the sinus. Thus the sinus may be like the sciatic nerve [8] in which either pressor or depressor reflexes may be elicited by stimulation at different frequencies.

There is a possibility that the carotid sinus played some part in Cushing's results. Thus, by increasing the resistance to the carotid flow, the increased intracranial pressure might elicit the direct pressor reflex of the sinus. The "vagus" effects spoken of by Cushing are also similar to those elicited by pressure in the neck, which, according to Heymans,[9] were noticed by Cooper in 1836, and by Morey in 1866, and, according to Cevolotto,[10] by Conato, in 1892. These effects from pressure in the neck have since been proved to have their origin in the carotid sinus. Also, if the carotid sinus plays a protective rôle to encephalic blood pressure, as Heymans and Bouckaert [11] suggested, should this protection not come into effect under conditions of increased intracranial pressure when the body is striving so hard to keep the blood pressure up to the necessary level? No work, as far as we know, has been done directly along these lines, but two different articles bear on the subject.

Heymans [12] studied the effect of increased intracranial pressure on the rate of the heart before and after denervation of the carotid sinus. A rise of intracranial pressure leads first to a slowing of the heart, then

2. Eyster, J. A. E.; Burrows, M. T., and Essick, C. R.: J. Exper. Med. **11**:489, 1909.

3. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe, Dresden, Theodor Steinkopff, 1927.

4. Heymans, C.: Le sinus carotidien et les autres zones vasosensibles réflexogènes, Paris, Presses Universitaires de France, 1929.

5. Danielopolu, D.; Marcu, I., and Proca, G. G.: (*a*) Klin. Wchnschr. **6**:2339, 1927; (*b*) Aslan, A.; Marcu, I., and Proca, G. G.: ibid. **7**:408, 1928.

6. Tomanek, Z.: Klin. Wchnschr. **7**:898, 1928.

7. Schroeder, E.: Klin. Wchnschr. **6**:110, 1927.

8. Martin, E. G., and Mendenhall, W. L.: Am. J. Physiol. **38**:98, 1915.

9. Heymans, C.: Rev. belge sc. méd. **1**:507, 1929.

10. Cevolotto, G.: Gior. med. d. Alto Adige **1**:37, 1929.

11. Heymans, C., and Bouckaert, J. J.: Compt. rend. Soc. de biol. **99**:1871, 1928.

12. Heymans, C.: Am. J. Physiol. **85**:498, 1928.

to a short acceleration, followed in turn by a marked slowing. Heymans raised intracranial pressure before and after denervating the carotid sinus and got the same effects. He concluded that the action of increased intracranial pressure is entirely central, in contrast to the slowing of the heart due to increased cephalic blood pressure, an effect which originates in the carotid sinus. This conclusion, we believe, is not entirely justified, because he should have considered that the aortic depressor zones were still intact, and that they had been shown to be able to assume part of the tone of the carotid sinus after its extirpation.

Izquierdo [13] studied the influence of the aortic and carotid sinus reflexes on the height and form of the rise of blood pressure produced by peripheral stimulation of the splanchnic nerves. If one assumes, as did Cushing, that the rise of blood pressure following increased intracranial pressure is due to a direct stimulation of the vasomotor center, this effects the rise mainly by the action of the splanchnic nerves. Therefore, in this case, conditions are analogous to those in our experiments.

Izquierdo stimulated the splanchnic nerves peripherally with a faradic stimulus and found that when he extirpated all four depressor zones (the two carotid sinus and the two aortic depressor zones), the blood pressure rose very much higher, and the curve was much simpler than before. He found also, by varying the set which he eliminated first, that contrary to general opinion, the carotid sinus reflexes contributed most to this depressor effect; i. e., their extirpation helped the rise of blood pressure more than the extirpation of the aortic depressor zones. Izquierdo showed that the carotid sinuses are the main factors in producing the dip in the splanchnic pressure curve. He also found that if one carotid sinus was extirpated, there was usually a difference in rise of blood pressure, sometimes a considerable one. He showed that if all four depressor zones were present, their joint inhibitory action was so great, in some cases, that stimulation of the splanchnic nerves had little effect. He believed that when part of the depressors were eliminated, the others would assume their tone to a greater or less degree. Izquierdo concluded that the mechanism of the increased blood pressure on stimulation of the splanchnic nerves was a result of two factors: (1) a factor of direct vasomotor stimulation, and (2) an indirect (secondary) depressor factor due especially to the carotid sinuses.

Hering [3] and Koch [14] remarked that removal of some of these nerves regulating blood pressure has resulted in a more intense function of the

13. Izquierdo, J. J.: J. Physiol. **70**:221, 1930.

14. Koch, E.: Die reflektorische Selbststeuerung des Kreislaufes in Kisch, Bruno: Ergebnisse der Kreislaufforschung. Dresden, Theodor Steinkopff, 1931.

remaining nerves. Cromer and Ivy [15] found that in dogs the physiologic rôle of the carotid sinus as a reflexogenic center for control of blood pressure can be readily taken over by other mechanisms.

EXPERIMENTS AND COMMENT

We have just completed a series of experiments on more than twenty dogs and rabbits, in which we used a somewhat modified combination of Cushing's and Hering's technics. We increased the cerebrospinal fluid pressure, at the same time varying the effect of the carotid sinus either by stimulation or by extirpation. Ether anesthesia with premedication by morphine was usually used, although the same results were obtained when ethylcarbonate (urethane) or phenobarbital sodium was used.

The apparatus was as follows: One arm of a specially constructed T-shaped metal cannula was introduced into the subarachnoid space, usually over the parietal area of the skull to minimize bleeding. This was screwed tightly into the trephine hole and thus kept air-tight. To the second arm of the "T" was attached a hose for flushing, this outlet being closed off with a clamp during the experiment. To the other arm was attached a long rubber hose running to a pressure bottle suspended on a pulley above the table. A side arm on this hose was connected to a mercury manometer which recorded the intracranial pressure on a kymograph.

The fluid used in the pressure bottle was an isotonic 0.9 per cent solution of sodium chloride which was kept at approximately 38 C. to avoid shock to the animal. The bottle was corked tightly, but the outlet at the bottom was left open, allowing the fluid to exert its pressure continuously on the contents of the subarachnoid space.

In the beginning of the experiment, the level of the fluid in the bottle was brought to the same height as the subarachnoid space of the dog, and the needle which recorded intracranial pressure was set at zero. Thus, to be more accurate, there would have to be added to our readings a figure corresponding to the normal intracranial pressure of the dog, which when taken with the dog lying down is much too small to be measured by the apparatus.

The cerebrospinal fluid pressure could then be increased up to a certain point by elevating the bottle on a pulley. If higher pressures were desired, the tension was further increased by pumping air over the fluid of the closed bottle, the bulb of an ordinary sphygmomanometer being used. The manometer needle writing this pressure on the drum recorded any changes in intracranial pressure.

Blood pressure was recorded from the femoral artery by cannulating it and connecting the cannula to a mercury manometer by a rubber tube. Respirations were recorded by a lever connected to a tambour strapped to the animal's chest. A stimulation recorder which was regulated by a foot pedal allowed the exact time of a manipulation to be recorded. Time was recorded usually in half minute intervals. All of these writing points were set in the same ordinate on the graph so that simultaneous readings could be obtained.

Before proceeding with the experiment, we isolated the carotid sinuses in the neck according to Hering's technic. A midline incision was made. The common carotid arteries were shelled out from below upward, and the internal and external

15. Cromer, S. P., and Ivy, A. C.: Proc. Soc. Exper. Biol. & Med. **28**:565, 1931.

carotids were separated from surrounding structures, care being taken to avoid injury to the numerous fine arteries and nerves in this region. One or two of the smaller vessels near the sinus were tied off in order to expose the sinus more completely. A thread around the external carotid allowed the sinus to be moved with no stimulation during the experiment.

Dry gauze was used to insulate the sinus from other structures during stimulation. Special care was taken to avoid unnecessary shock, and time was always allowed after manipulation for the animal's nervous system to recover. In certain cases we isolated the nerves, by either cutting or stimulating them according to Hering's technic.

The carotid sinuses were first stimulated both electrically and mechanically to prove that they were intact and working normally, and to see how much reaction the individual animal gave.

Intracranial pressure was then increased by introducing the warm physiologic solution of sodium chloride into the cerebrospinal space by increasing the pressure in the bottle. Usually the pressure was increased in stages. In most experiments it was increased gradually, although sudden changes were occasionally used for comparison. The rapidity of change was found to make very little difference, except for the fact that the more gradual change avoided most of the effects described by Cushing as vagal.

On raising intracranial pressure with the carotid sinuses intact, we observed much the same results as did Cushing. When the intracranial pressure was raised, the blood pressure rose, and in some cases, the needle used to test the blood pressure was pushed above the limits of our recording apparatus without any signs of failure (over 350 mm.). The height to which the blood pressure could be raised in this way evidently depended on the individual reaction of the dog, the extent of shock and the degree of anesthesia. In some dogs the blood pressure would fail quite soon, that is, climb a short distance and suddenly fall rapidly, following which the animal would die of respiratory failure unless the intracranial pressure was immediately lowered and artificial respiration instituted. On lowering the intracranial pressure toward normal, the reverse effect, a lowering of blood pressure, was observed. Chart 2 *A* presents the records for an animal in which such effects were obtained.

Our main experiments, however, were in testing the responses of the carotid sinus during this increased cerebrospinal fluid pressure. When the intracranial pressure was at different levels, that is, below, on a level with, or above blood pressure, the carotid sinuses were stimulated, either electrically or mechanically. When this was done, even if the intracranial pressure was greater than the blood pressure, stimulation of the sinus always produced a fall of blood pressure. This fall of pressure was usually greater than that which would occur under normal conditions of intracranial pressure.

In chart 1 the intracranial pressure had been raised above the blood pressure, but before the blood pressure responded, the carotid sinus was stimulated electrically. The blood pressure went down much more

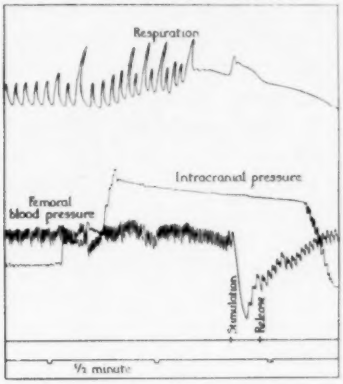

Chart 1.—Stimulation of the left carotid sinus under increased intracranial pressure.

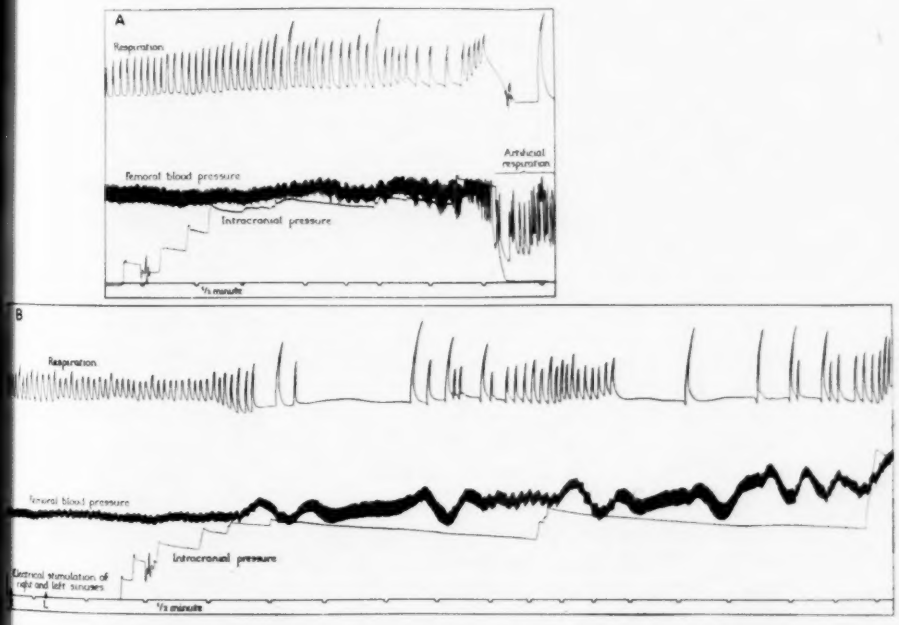

Chart. 2.—*A*, showing the weakness of response and the early failure of the blood pressure when both sinuses are intact; *B*, showing greater response and no failure of the blood pressure when both sinuses are denervated; same animal as in *A*.

than it had before with the same intensity of stimulation when the intracranial pressure was normal. The same result occurred almost constantly with increased intracranial pressure, even when this was considerably below the level of the blood pressure.

The experiments of raising intracranial pressure after denervation of the sinuses were even more conclusive. In these experiments, a graph of the effect of increased intracranial pressure was made in the usual way. The carotid sinuses were denervated thoroughly in the following manner. Hering's nerve, if found, was cut, and the artery was stripped of all excess tissue and carefully painted with 5 per cent

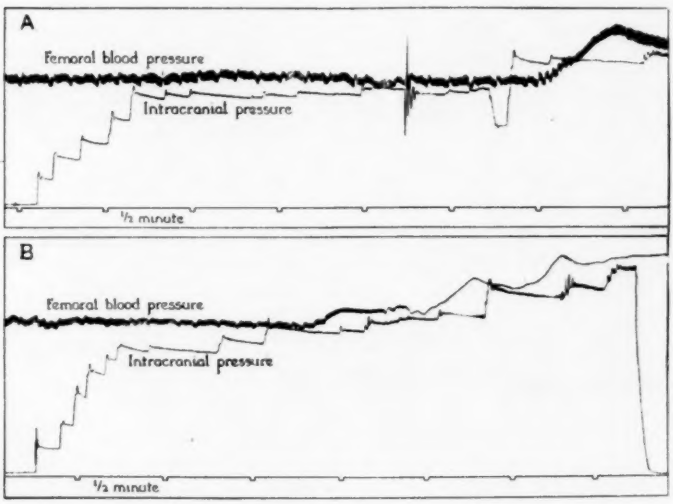

Chart 3.—*A*, showing the weakness of the response of blood pressure when both sinuses are intact. *B*, same animal as in *A*; the results when both common carotid sinuses are clamped off.

phenol. After allowing time for the shock to wear off, we repeatedly stimulated the carotid sinus with a strong electrical current. If we could get no effect either on respiration or on blood pressure, we believed our denervation was complete and proceeded with the experiment.

Then, when the reflexes of the carotid sinus were destroyed, we repeated the raising of intracranial pressure in the same manner as when they were intact. In practically every case, the rise of blood pressure was greater than before (chart 2*B* and 3*B*). In no case was the response less, although the animal was of course in poorer condition than previously.

The blood pressure rose more promptly and to greater height after the intracranial pressure had approached it than before denervation occurred, and failure of the vasomotor mechanism did not appear to occur as early. The blood pressure also went up before the intracranial pressure approached as closely to it as it did earlier, when the sinuses were intact.

Chart 2 shows a representative experiment of this type. In 2 *A* is shown the very weak and feeble action of the blood pressure in overcoming intracranial pressure. In fact, the intracranial pressure had to be raised above the blood pressure before the latter would rise. The blood pressure rose very little before the vasomotor center failed, and then the blood pressure fell rapidly. Immediate lowering of the intracranial pressure and artificial respiration were necessary to save the animal's life. On the same dog (chart 2 *B*), however, after denervating the carotid sinuses, the blood pressure went up much more easily and did not fall so soon, and a greater difference between these two pressures was maintained. After the intracranial pressure had been lowered and had remained at normal for some time, the carotid sinuses were again stimulated to make sure of their denervation.

These results remind one of Izquierdo's findings. He found that in some cases the depressor action was so strong that very little increase of blood pressure resulted from stimulation of the splanchnic nerves. Eyster, Burrows and Essick remarked that in some of their animals very little increase of blood pressure resulted from increased intracranial pressure and early failure was seen.

In other experiments we shut off the common carotids below the carotid sinuses. The results were the same as when the carotid sinuses were eliminated by the method of denervation. This is illustrated by chart 3 *A* and *B*. The response of the blood pressure is somewhat better to start with than in chart 2.

The same experiments were performed on three rabbits. In addition to denervation of the sinuses, the depressor nerves in the neck were also cut. The difference before and after denervation of these four depressor areas was not very great, but always, as in the dogs, the response tended to be better than before denervation. The responses, however, even in normal rabbits, were not so satisfactory or so conclusive as in dogs.

These results, which in our series were quite constant, lead us to believe that the carotid sinus is not primarily concerned with the mechanism described by Cushing; his conclusion that the mechanism is a central one, probably effected by anemia of the medullary centers, seems to hold true. The carotid sinuses as well as the aortic depressor areas must act secondarily on the centrally increased blood pressure and tend to lower it. It is striking that, although the differences we found

before and after the denervation of these depressor zones were, in some cases especially, not great, they were always in the same direction, the response tending to be better after these brakes were out of the way. In other words, in these experiments the blood pressure acts much the same as in Izquierdo's experiments, except that in our experiments the vessels were constricted by the increased intracranial pressure (anemia) stimulating the centers, while in Izquierdo's experiment the constriction was due to electrical stimulation of the splanchnic nerves. The increased intracranial pressures have little if any direct effect on the reflexes of the carotid sinuses, which tend to inhibit the vasomotor and respiratory centers and stimulate the cardio-inhibitory center. All of these effects are produced when the blood pressure begins to rise in the normal animal and work against the rise of pressure necessary to supply the brain with blood. One might expect a greater difference in effect after elimination of the sinuses than was actually found, but in the dogs the aortic depressors were still present, and rabbits do not stand the severe operation and long anesthesia very well. In our experiments, we found no evidence that the sinuses ever act as pressor mechanisms and thus help the centers receive the blood they need. The anemia of the centers is the stronger and more fundamental condition and overcomes the secondary depressor reflexes caused by the rise of pressure. These secondary reflexes are sometimes nearly able to overcome the primary effects.

Although in lower animals only depressor effects have been found from stimulation of the sinus by pressure, in man and apes, pressor effects have been obtained [5] in certain cases from such stimulation. It has been suggested that these pressor results might have been due to pressing on the carotid artery below the sinus, which thus lowered the pressure in the sinus. We do not think this is the true explanation, as the levels of stimulation were varied.[5a] We believe the evidence points to the fact that the sinus in man and apes is, as Danielopolu [5b] puts it, amphoteric. It may be analogous to a peripheral nerve in cases in which it has been shown [8] that pressor, depressor or mixed results can be produced by altering the strength and the rhythm of the stimulus. In our experiments, even though an emergency existed, no evidence of a pressor effect was found. There is a certain amount of evidence that in dogs very low pressures may actually stimulate pressor mechanism and not merely produce its effect from a dropping out of the depressor mechanism. No one seems to have found that this pressor mechanism was stimulated by high pressures, as may happen in man and apes.

In doing these experiments, we made a number of incidental observations. The first striking thing we noticed was how close the intra-

cranial tension could be brought to the mean blood pressure before a rise of blood pressure resulted. Tzanck and Renault [16] stated their belief that the venous pressure and the cerebrospinal fluid pressure are almost the same, the latter varying with the former. Consequently, it is interesting to note how small a difference could exist between arterial pressure and venous pressure before sufficient anemia of the medullary centers resulted to cause a cessation of respiration or an increase of blood pressure. This difference seemed to increase after extirpation of the carotid sinuses. In most animals these centers seem to be able

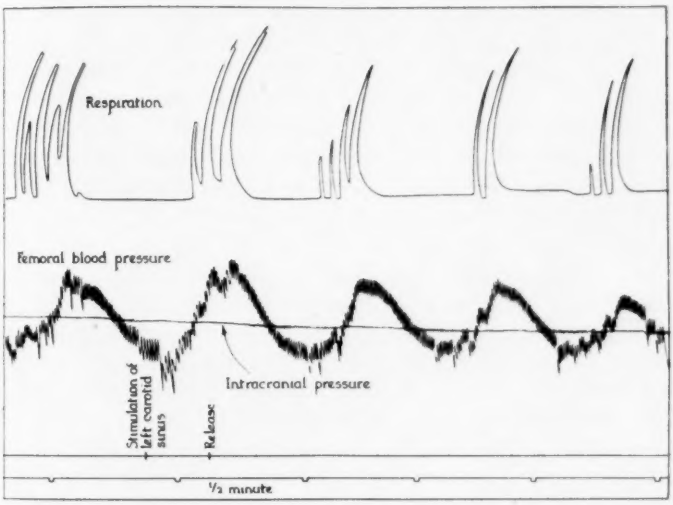

Chart 4.—The Traube-Hering waves and the Cheyne-Stokes respiration under increased intracranial pressure.

to get along with a very poor supply of blood provided the blood is properly arterialized.

Another observation was the great variability shown by different animals both as to the increased intracranial pressure and as to the carotid stimulation. Some could stand increases of intracranial pressure many times the original value, while in others the vasomotor mechanism collapsed very readily. This, of course, was influenced by the condition of the animal and the anesthesia.

As Cushing found, sometimes very prominent Traube-Hering waves and Cheyne-Stokes respiration resulted. Cushing explains these as being due to a poor condition of the respiratory center, which in this case

16. Tzanck, A., and Renault, P.: Compt. rend. Soc. de biol. **96**:157, 1927.

would be caused by lack of nourishment due to the increased intracranial pressure. In some cases, the high point of the blood pressure would be above the intracranial pressure and the low point below the intracranial pressure, and as a result, Cheyne-Stokes respiration would result, the hyperpnea occurring when the blood pressure was above the intracranial pressure and the apnea when it was below, as shown in chart 4.

On some of our graphs the curve for intracranial pressure showed marked oscillations of the same spacing as those of respiration. This increase in expiration and decrease in inspiration of intracranial pressure has been noted by others before (Cushing [1] and Golla and Symes [17]). Cushing explains it by pulsation of the brain, which, he says, is greater the higher the intracranial pressure.

In these experiments we took the opportunity to verify some of the results on the carotid sinus which many investigators have obtained. On simple stimulation of the sinus we got the typical depressor effect: slowing of the heart and respiration with a fall in blood pressure. What was peculiar to us was that in some dogs the blood pressure effect was pronounced and the respiratory effect slight, while in others the reverse held true.

CONCLUSIONS

1. The rise of arterial pressure following an increase of intracranial pressure is, in dogs and rabbits, of central origin, as Cushing thought, and does not start in the carotid sinus. In our experiments the carotid sinus was always found to act as a depressor zone tending to keep the pressure down even when the centers needed blood.

2. Following denervation of the sinus, increased intracranial pressure caused a more prompt and greater rise of arterial pressure. The differences before and after denervation were not very great, and the same was true in rabbits in which the influences of the aortic depressors also were removed.

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17. Golla, F. L., and Symes, W. L.: J. Physiol. **50**:32, 1916.

ABSORPTION OF DEXTROSE BY RECTUM

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AND
LOUIS C. BOAS, M.D.
BROOKLYN

A recent paper by Scott and Zweighaft [1] has again raised a long-standing controversy on the question of the absorption of dextrose by rectum. They have demonstrated in a series of studies on fifty medical students that there is no evidence of the absorption of dextrose when it is given in a 10 per cent concentration (40 Gm.). The literature disclosed a marked difference of opinion regarding the absorbability of dextrose administered by this route. In view of the therapeutic importance of the answer to this question, the authors have attempted an investigation of this problem in an unselected series of diabetic and nondiabetic patients in a hospital ward.

The following investigators found evidence that dextrose is absorbed when it is instilled into the rectum. Schoenborn [2] showed that there was a maximum absorption of dextrose in from one to two hours. Von Leube [3] found 63 out of 70 Gm. absorbed, mostly in one hour. Müller [4] obtained an absorption of 50 per cent of the amount instilled in two hours. Reach [5] was one of the earliest investigators to demonstrate a rise in the respiratory quotient after the rectal instillation of dextrose, and he concluded that there is a slight absorption. Others who found an elevation in the respiratory quotient and confirmed Reach's observations were Bergmark,[6] Hári and von Halász,[7] Fleming [8] and Car-

From the Medical Service of Dr. J. N. Cohen and the Laboratories of the Greenpoint Hospital.

1. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following the Rectal Administration of Dextrose, Arch. Int. Med. **49**:221 (Feb.) 1932.

2. Schoenborn: Zur Frage der Resorption von Kohlehydraten im menschlichen Rectum, Dissert., Würzburg, 1897.

3. von Leube, in Leyden: Handbuch der Ernährungstherapie und Diätetik, Leipzig, Georg Thieme, 1903, vol. 1, 496.

4. Müller: Verhandl. d. Kongr. f. inn. Med., 1898, p. 454.

5. Reach: Arch. f. exper. Path. u. Pharmakol. **47**:231, 1902.

6. Bergmark: Skandinav. Arch. f. Physiol. **32**:335, 1915.

7. Hári, P., and von Halász, A.: Die Therapie des Diabetes mellitus mit Zuckerklystieren, Dissert., Kiel, 1917.

8. Fleming: J. Physiol. **53**:236, 1919.

penter.[9] Deucher,[10] Zemisch,[11] Stölting,[12] Hausmann,[13] Orlowski [14] and Bergmark [6] reported that the absorption of dextrose varied from 50 to 89 per cent of the amount introduced. Von Halász [15] obtained marked absorption, especially when the the dextrose was given in high concentration. Satta [16] attempted to prevent diabetic acidosis with the administration of dextrose rectally, and he maintained that he was successful. Hubbard and Wilson [17] obtained sufficient absorption to decrease the excretion of acetone following a diet high in fat content. Lüthje [18] obtained marked absorption, and he demonstrated a rise in blood sugar. Tallerman [19] gave 60 Gm. in 180 cc. of a saline solution. He found a maximum rise of blood sugar of 62 mg., with an average of 19 mg., and he concluded that some dextrose is absorbed. Levi [20] confirmed Tallerman's observations, but stated that there is a slight and slow absorption. He did not analyze the return of the enema. Julesz and Winkler [21] showed that hyperglycemia occurred twenty minutes after 500 cc. of a 20 per cent solution of dextrose was given to normal subjects.

Among those who were unable to demonstrate evidence of absorption were Rosenfeld,[22] Janson-Blohm [23] and Rubino and Varela.[24] Pressman [25] studied this problem in seven human subjects. He administered 240 cc. of a 30 per cent solution of dextrose and found that the blood sugar was at or below the fasting level ninety minutes later. He recovered 24 per cent after four hours. He maintained that a large

9. Carpenter, T. M.: Human Metabolism with Enemata of Alcohol, Dextrose and Levulose, Washington, D. C., Carnegie Institution, 1925.

10. Deucher: Cor.-Bl. f. schweiz. Aertze **33**:41, 1903.

11. Zemisch: Ausnutzung von Nährklystieren, Halle, 1903.

12. Stölting: Ueber den Wert verschiedener Zuckerarten als Bestandteil von Nährklystieren, Dissert., Halle, 1904.

13. Hausmann: Experimentelle Untersuchungen über die Ausnutzung verschieden zusammengesetzter Zuckerclysmen, Dissert., Halle, 1905.

14. Orlowski: Ztschr. f. diätet. u. physik. Therap. **8**:481, 1905.

15. von Halász: Deutsches Arch. f. klin. Med. **98**:433, 1910.

16. Satta: Beitr. z. chem. Physiol. u. Path. **6**:376, 1905.

17. Hubbard and Wilson: Proc. Soc. Exper. Biol. & Med. **19**:292, 1922.

18. Lüthje, H.: Therap. d. Gegenw. **54**:193, 1913.

19. Tallerman, K. H.: Quart. J. Med. **13**:356, 1920

20. Levi, D.: Brit. J. Surg. **15**:282, 1927.

21. Julesz and Winkler: Ztschr. f. d. ges. exper. Med. **80**:823, 1932.

22. Rosenfeld: Berl. klin. Wchnschr. **44**:1663, 1907.

23. Janson-Blohm: Upsala läkaref. förh. **20**:331, 1915.

24. Rubino and Varela: Klin. Wchnschr. **1**:2370, 1922.

25. Pressman, J.: Am. J. M. Sc. **179**:520, 1930.

portion of the amount not accounted for represented a loss due to bacterial fermentation, and he believed that the depression of the blood sugar was due to the stimulation of the insulin-producing islets by the hormone action of a small amount of absorbed dextrose. He also quoted Brugel, who found, after five hours' incubation, the disappearance of 34 per cent of dextrose subjected to fermentation in feces.

METHOD

Patients in the ward, including both male and female and diabetic and nondiabetic persons, who had no complicating rectal disorders were used for our study. Among the nondiabetic group no patients were used in whom any metabolic

Table Showing the Effect of the Rectal Administration of Dextrose on the Blood Sugar

Number of Cases	Amount of Dextrose Instilled	Average Fasting Blood Sugar, Mg.	Blood Sugar Rise Above Fasting			Per Cent Rise in Blood Sugar	Deviation in Duplicate Determination	Dextrose Recovered				Per Cent Absorbed
			Maximum	Minimum	Average			Maximum	Minimum	Average	Per Cent	
Nondiabetic												
11	250 cc. 10% (25 Gm.)	83	47	3	17	21	±2%	11.2	1.7	6.2	27	73
7	200 cc. 25% (50 Gm.)	83	50	2	14	17	±2%	14.6	4.0	9.2	18	82
5	400 cc. 5% (20 Gm.)	86	34	2	14	16	±2%	3.0	0.9	2.1	10	90
1	200 cc. 50% (100 Gm.)	90	..	..	22	25	±2%	....	...	18.3	18	82
Diabetic												
1	250 cc. 10% (25 Gm.)	312			66	21	±4%			9.4	38	62
1	250 cc. 10% (25 Gm.)	123			11	9	±2%			10.2	41	59
1	200 cc. 25% (50 Gm.)	140			4	3	±3%			6.0	12	88
1	200 cc. 25% (50 Gm.)	220			4	2	±3%	Evacuation,		10.7	21	79
1	400 cc. 5% (20 Gm.)	179	Decreased		35	..	±3%	1 hr.		2.7	14	86
1	400 cc. 5% (20 Gm.)	145			73	50	±3%			1.2	6	94
1	400 cc. 5% (20 Gm.)	237			88	38	±4%			2.7	14	86

disorder was found or suspected. Experiments were performed when the patient was in a fasting state in the morning, fourteen hours after a previous meal. A cleansing enema was first given, which was followed by an effective evacuation of the bowel. Blood was then drawn and citrated. One hour after the enema, dextrose was instilled into the rectum in amounts which ranged from 20 to 100 Gm. in various concentrations. The dextrose was uniformly dissolved in distilled water. It required approximately a minute to instill this solution. Specimens of blood were then drawn at intervals of thirty, sixty and one hundred and twenty minutes after the instillation. Estimations of the blood sugar were performed in duplicate by the Folin-Wu method. No results were accepted when the duplicate deviation was more than 3 per cent. The series consisted of twenty-four nondiabetic patients, eleven of whom received 250 cc. of a 10 per cent dextrose (25 Gm.); seven, 250 cc. of a 25 per cent solution (50 Gm.); five, 400 cc. of a 5 per cent solution (20 Gm.), and one, 200 cc. of a 50 per cent solution (100 Gm.). Two of the diabetic patients received 250 cc. of a 10 per cent solution of dextrose (25 Gm.); two, 200 cc. of a 25 per cent solution (50 Gm.), and three, 400 cc. of a 5 per cent solution (20 Gm.).

At the end of two hours the patients were given an enema with 500 cc. of tap water, and the evacuation was collected. These returns were analyzed for the dextrose content by the Benedict quantitative method for estimations of sugar in the urine.

RESULTS

The accompanying table is a composite picture of the effect of the rectal administration of dextrose on the blood sugar, and it also indicates the percentage of sugar absorbed. The cases are grouped accord-

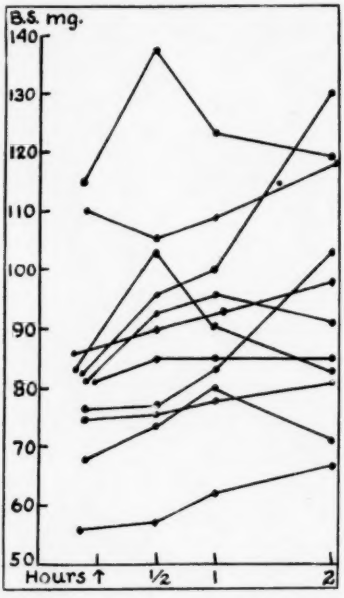

Chart 1.—Results of the administration of dextrose in nondiabetic patients; 250 cc. of a 10 per cent solution of dextrose (25 Gm.) was administered by rectum. The average amount of blood sugar recovered was 6.8 Gm.

ing to the amount and concentration of dextrose given. The upper part of the table shows the results in nondiabetic persons, while the lower part contains the study on diabetic patients. One observes that in the nondiabetic group there is a rise in the blood sugar ranging between 16 and 25 per cent, and that the amount of dextrose recovered at the end of the experiment varies between 10 and 27 per cent at the end of two hours. This indicates that as much as 90 per cent of the dextrose administered by rectum was absorbed. In the diabetic group, much the same picture prevails, except for the fact that two patients showed no rise in blood sugar, and one even experienced a 20 per cent

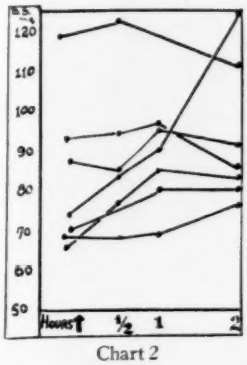

Chart 2

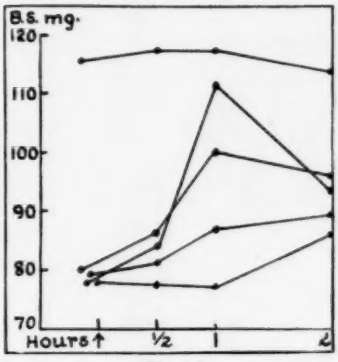

Chart 3

Chart 2.—Results in nondiabetic patients in whom 200 cc. of a 25 per cent solution of dextrose (50 Gm.) was administered by rectum. The average amount of blood sugar recovered was 9.2 Gm.

Chart 3—Results in nondiabetic patients in whom 400 cc. of 5 per cent solution of dextrose (20 Gm.) was administered by rectum. The average amount of blood sugar recovered was 2.1 Gm.

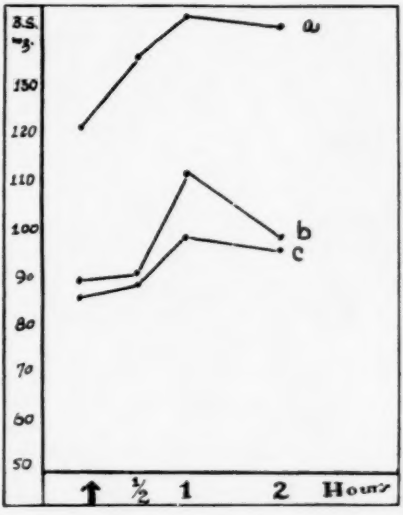

Chart 4.—Results in nondiabetic patients: (*a*) given 200 cc. of a 5 per cent solution of dextrose (10 Gm.); recovered, 0.8 Gm.; (*b*) given 200 cc. of a 50 per cent solution of dextrose (100 Gm.); recovered, 18.3 Gm.; (*c*) given 200 cc. of a 5 per cent solution of dextrose (100 Gm.); recovered, 0.0 Gm.

depression. The other four diabetic patients had elevations in the blood sugar of 9, 21, 38 and 50 per cent. All, however, showed evidence of absorption by the analysis of the rectal return. In the patient in whom there was a depression in the blood sugar, only 14 per cent of the amount administered could be recovered at the end of two hours.

Chart 1 is a graphic representation of the results in the nondiabetic persons who received 250 cc. of a 10 per cent solution of dextrose

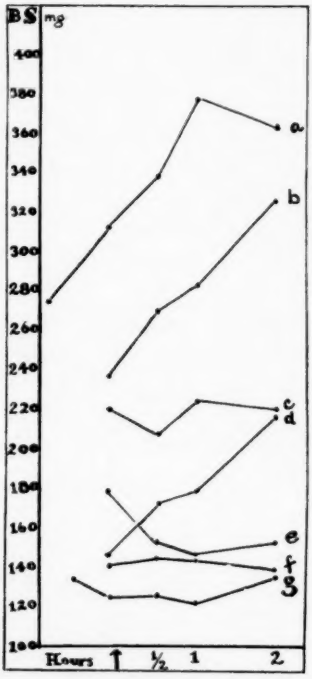

Chart 5.—The results of the administration of dextrose solution in diabetic persons are as follows: (*a*) with 250 cc. of a 10 per cent solution of dextrose (25 Gm.) administered, 9.4 Gm. of blood sugar was recovered; (*b*) with 400 cc. of a 5 per cent solution of dextrose (20 Gm.), 2.7 Gm.; (*c*) with 200 cc. of a 25 per cent solution of dextrose (50 Gm.), 9.0 Gm.; (*d*) with 400 cc. of a 5 per cent solution of dextrose (20 Gm.), 1.2 Gm.; (*e*) with 400 cc. of a 5 per cent solution of dextrose (20 Gm.), 2.7 Gm.; (*f*) with 200 cc. of a 25 per cent solution of dextrose (50 Gm.), 6.0 Gm., and (*g*) with 250 cc. of a 10 per cent solution of dextrose (25 Gm.), 10.2 Gm.

(25 Gm.). One observes a general tendency for the curves to rise; some rise at the end of thirty minutes, but most of them show a delayed rise,

reaching the maximum level at the end of two hours. Chart 2 shows the delayed rise with 200 cc. of a 25 per cent solution of dextrose (50 Gm.). Chart 3 shows a similar phenomenon with 400 cc. of a 5 per cent solution of dextrose (20 Gm.). Chart 4 shows the results in a patient who received 200 cc. of a 50 per cent solution of dextrose (100 Gm.) and in two patients who were given 200 cc. of a solution of dextrose (10 Gm.). All of the patients showed the same general tendency. Chart 5 is a graphic summary of the studies made with diabetic patients. Three show no rise and four a delayed elevation.

COMMENT

The purpose of this investigation was to determine, in the face of complicating opinions, whether or not dextrose can be absorbed by rectum. We were not particularly interested to know whether absorption, if it did occur, was equal in rate and degree to that occurring when dextrose was given by the oral route. It was important to determine whether a patient to whom dextrose could not be administered orally and for whom the parenteral route was contraindicated could derive the benefits of dextrose when it was in contact with the large bowel. This question is one of therapeutic importance and requires a definite answer. The literature discloses evidence that there is an elevation in the respiratory quotient following the rectal administration of dextrose and clearly indicates that dextrose given in this manner was not only absorbed but utilized.

Pressman's statement that the dextrose not accounted for in the enema return at the end of the experiment could have undergone bacterial fermentation cannot be accepted by us. While he maintains that 34 per cent of the dextrose can disappear by fermentation with feces in five hours, we found that in one patient who evacuated the dextrose enema at the end of one hour only 8 to 25 Gm. given was returned, indicating that 68[8] per cent was not accounted for in an hour. This period was not long enough to allow for fermentation. It also cannot account for the disappearance of as much as 90 per cent of the dextrose in two hours.

Further evidence that dextrose is absorbed in significant quantities is illustrated by the fact that a diabetic patient who had recently experienced an attack of hypoglycemia as the result of an overdosage of insulin was immediately relieved by the administration of 25 Gm. of dextrose by rectum. Dextrose was given in this manner by the intern because the patient's jaw was rigid from the tetanic syndrome asso-

ciated with a state of hypoglycemia, and he found considerable difficulty in inserting the needle into a vein, making it necessary to administer the dextrose by rectum.

CONCLUSIONS

1. Dextrose is absorbed when it is administered by rectum.

2. Although dextrose does not pass through the membrane of the colon as rapidly as through the small intestine, a sufficient amount is absorbed to warrant recognition of this method as an acceptable therapeutic procedure.

9 Prospect Park West.

PLEURISY IN RHEUMATIC FEVER

CLINICAL OBSERVATIONS

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Pleural involvement in rheumatic fever is an important episode in the course of the disease. Lesions may result from some complication, such as myocardial failure or pulmonary infarction, or may be due to the disease itself, as are the more common involvements of the synovia, myocardium, endocardium and pericardium. Fifteen cases of rheumatic fever in which there was undisputed evidence of pleural involvement have been studied. For purposes of discussion we have divided them into two groups: (1) thirteen cases of true rheumatic pleurisy and (2) two cases of bilateral hydrothorax accompanying myocardial failure.

FIBRINOUS PLEURISY

CASE 1.—A girl, 15 years of age, was admitted to the hospital, complaining of a sharp pain in the left axilla, which was increased in severity on inspiration. Six years and three years previously she had had rheumatic fever. Twelve days before admission, following recovery from a mild cold in the head, she was seized by a sudden, severe, stabbing pain in the left axilla, which lasted a few hours. The pain was increased on inspiration. On the following morning she complained of general malaise and moderately severe pain and swelling of all her joints; she had a temperature of 102 F. With salicylate therapy, the pain in the joints immediately subsided and the temperature returned to normal. Five days before entering the hospital, the sharp, severe pain in the anterior left axilla recurred. It persisted, but was described at the time of admission as being dull, except on inspiration, when the pain became knifelike. There had not been cough, sputum or hemoptysis.

Tonsillectomy and adenoidectomy had been performed immediately after the first attack of polyarthritis. The patient had rarely had sore throat. Her general health had been good, except for the recurrent attacks of rheumatic fever.

At the time of admission to the hospital, the temperature was 104.4 F.; the pulse rate was 100, and respirations were 24 per minute. The patient was well developed and fairly well nourished. A small amount of tonsillar tissue was noted on the left side of the throat, and the pharynx was slightly injected. The submaxillary lymph nodes were slightly enlarged but were not tender. Respiratory excursions of the chest were limited. In the left axilla the percussion note was dull; the voice and breath sounds were only faintly heard and tactile fremitus was

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absent. Over the area of dulness in the left axilla a friction rub was detected. On percussion, the heart was not found to be increased in size. The first sound, at the apex, was snapping in character; the second sound, over the pulmonic area, was accentuated; a short systolic murmur was heard just inside the heart's apex. Physical examination revealed no other abnormality.

On the sixth day after entry, the temperature reached normal. The signs and symptoms referable to the chest gradually decreased with the fall in temperature. Salicylates were not given until after the cessation of fever and the disappearance of signs in the chest. The patient remained asymptomatic. A blowing diastolic murmur over the base of the heart was heard during the last two weeks of the four weeks in the hospital. Roentgenologic studies at the time of entry showed fine mottling throughout the pulmonary fields but no evidence of fluid at the base of either lung. The heart showed a mitral deformity. Later studies showed the pulmonary fields to be clear. Electrocardiographic studies showed the QRS complex to be slurred and the T waves to be flat in all leads. The leukocyte count was 20,200 per cubic millimeter at the time of admission, and 8,100 at the time of discharge. The urine was normal. Examinations of the sputum gave repeatedly negative results for tubercle bacilli.

The case was one of recurrence of rheumatic fever, with unilateral fibrinous pleurisy accompanied by evidence of pulmonary changes.

The clinical pictures in cases 2 and 3, in which unilateral fibrinous pleurisy occurred during the course of a recurrence of the acute manifestations of rheumatic fever, were similar. The extension of the process to the pleura was accompanied by sharp, stabbing pain in the chest, which was increased on movement of the wall of the chest, and by the presence of a pleural friction rub. The duration of the signs and symptoms was relatively short. There was a subsidence of the process without clinical evidence of the development of fluid in the pleural spaces.

The occurrence of jaundice in one patient presented a difficult diagnostic problem. It was impossible to decide whether there was an associated catarrhal jaundice or whether the pulmonary process was sufficient to lead to hepatitis. It was not thought that pulmonary infarction was a logical explanation in this case. Bezançon and Weil [1] reported a case in which there were pericarditis and pleuritis during the course of an acute attack of rheumatic fever in a patient with jaundice. Klemperer, Killian and Heyd [2] discuss this subject.

RHEUMATIC PLEURISY WITH EFFUSION

CASE 5.—An Irishman, aged 28, complained of pain in the joints for nine days before entry to the hospital. He had come to the United States five months previously. At the age of 13, and again, at the age of 19, he had been in a

1. Bezançon, F., and Weil, M. P.: La maladie rhumatismale cardiopathie chronique à poussées successives sur le système séreux, Ann. de méd. **19**:92 (Feb.) 1926.

2. Klemperer, P.; Killian, J. A., and Heyd, C. G.: The Pathology of "Icterus Catarrhalis," Arch. Path. **2**:631 (Nov.) 1926.

hospital for several months because of rheumatic fever. His symptoms had been relieved by salicylates. He had been told that he had "heart trouble." Tonsillitis had been infrequent. One month before admission, he had a severe sore throat, which subsided promptly, but recurred slightly several times during the intervening month. Two weeks later, his ankles became painful and swollen, but the pain and swelling had subsided within twenty-four hours, so that he was able to return to work. Nine days before admission, the ankles became so painful and swollen that he was confined to bed. His temperature was elevated and many joints were swollen. For six days he was dyspneic and orthopneic and had a disturbing paroxysmal cough productive of small amounts of tenacious material. He had had several mild epistaxes.

At the time of entry, the temperature was 103 F., the pulse rate, was 102 per minute, and the respiratory rate was 28. The patient was well nourished, moderately well developed, slightly dyspneic and orthopneic. The facial expression was one of anxiety. The skin was warm and moist. There was a slight cyanosis of the lips and nail beds. The tonsils were red and inflamed. The respiratory excursions were symmetrical but shallow. Examination of the left lung revealed a few coarse, crackling râles at the base posteriorly. The percussion note over the right base posteriorly and below the right clavicle anteriorly was impaired. Tactile fremitus and voice sounds were increased, and bronchovesicular breath sounds occurred over these areas. On percussion the heart was found to be slightly enlarged. The outline was that of a mitral deformity. The first sound, at the apex, was snapping; the pulmonic second sound was accentuated; a blowing systolic murmur was heard over the apical region and a short, high-pitched, mid-diastolic murmur was heard inside the apex. The systolic blood pressure was 90; the diastolic, 60. The edge of the liver was palpable on deep inspiration. The elbows, knees and ankles were swollen, tender and slightly painful on motion.

On the day after entry, the roentgenologic study showed patchy density throughout both lungs, which was more marked in the right lung. On the following day, a pericardial friction rub was heard over the base of the heart, which was later audible over the whole precordium. The pericardial friction rub persisted for two and a half months. The signs over the lungs remained the same for ten days, when a pleural friction rub and bronchial breath sounds were heard in the left axilla and signs of a considerable amount of fluid appeared gradually at the right base. Seven hundred and seventy-five cubic centimeters of pinkish yellow fluid was removed from the right side of the chest. Clot formation was noted within ten minutes. There were 4,100 red blood cells per cubic millimeter, and 1,250 leukocytes, of which 32 per cent were polymorphonuclears and 68 per cent were lymphocytes. The fluid on bacteriologic culture remained sterile. The signs of patchy consolidation at the base of the right lung persisted for a week. There was clinical and roentgenologic evidence of a small amount of fluid at the bases of both lungs for another week. The temperature remained elevated for a month after the patient's admission, returning to normal gradually a week after pleurocentesis.

In spite of the administration of 100 grains (6.4 Gm.) of sodium salicylate, the joint symptoms were not entirely relieved while there was clinical evidence of pulmonary and pericardial lesions. There was no demonstrable effect of the salicylate therapy on the pulmonary and pericardial lesions. The pulse rate remained elevated for three months. Respirations remained between 28 and 36 per minute throughout the four weeks during which there were obvious pleural and pulmonary lesions. Convalescence was uneventful. Seventeen weeks later, at the time of the patient's discharge, the lungs and pleura showed no evidence of lesions, either clinically or roentgenologically. The heart at this time showed a

transverse diameter of 14 cm.; the inner diameter of the chest was 28.3 cm. The mid-diastolic murmur had disappeared. Of several electrocardiographic examinations, one showed left ventricular predominance.

The leukocyte count on entry was 21,450, of which 89 per cent were polymorphonuclear leukocytes. The leukocyte count became normal after six weeks in the hospital; at the time of the patient's discharge it was 8,500, of which 55 per cent were polymorphonuclears. On entry, the red blood cells numbered 4,220,000 and the hemoglobin (Sahli) was 70 per cent. These decreased within six weeks to 3,600,000 and 62 per cent respectively. The urine showed a slight trace of albumin, occasional granular casts and red blood cells during the period of hyperpyrexia. There was no growth in four blood cultures. Sputum culture yielded Streptococcus viridans at the time of the patient's entry to the hospital.

This patient, who was seen in his third attack of rheumatic fever, when admitted showed polyarthritis, myocarditis, probable active endocarditis and pneumonitis. After admission, signs of fibrinous pericarditis and bilateral pleurisy, at first characterized by friction rub and then by bilateral effusions, appeared.

In all, ten patients were studied in whom the usual course was the development of pleural effusion following fibrinous pleurisy. Pleurisy in these patients lasted for weeks or months, in contrast to a period of days in the three patients in whom the lesion was only of a fibrinous nature.

Of the thirteen patients with rheumatic lesions of the pleura, the youngest was 15 years of age. Five patients were over 30 years.[3] The proportion of males to females was 10:3.

Coburn [4] has remarked on the rather high incidence of rheumatic fever in the immigrant classes, and thus it is to be noted that four of the six foreign-born patients had had no evidence of rheumatic fever prior to their arrival in this country. The other two patients had a recurrence of rheumatic fever soon after their arrival in America. Five other patients were the offspring of recent immigrants.

Cultures of venous blood were made in ten of the thirteen cases. In twenty-eight instances the cultures remained sterile. In one culture, Streptococcus viridans was obtained, but five additional blood cultures from this patient remained sterile.

HYDROTHORAX

CASE 14.—An American youth, 20 years of age was admitted to the hospital, complaining of painful, swollen joints. He had been treated in the hospital on four previous occasions for rheumatic fever; at the time of the first admission he had been 12 years of age. In the succeeding five years he was followed during several

3. Patients who are admitted to the wards of the medical services of the Boston City Hospital are 12 years of age or older, which accounts for the absence of children in this series.

4. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams and Wilkins Company, 1931.

recurrences of polyarthritis and one attack of Sydenham's chorea. The development of the signs of a mitral disease were observed. During the three years preceding his fifth and last admission he had been free from symptoms; he had continued in school and had played baseball, football and hockey. Ten days prior to the last entry, a severe sore throat developed, which was followed by pain, tenderness, redness and swelling of the ankles, knees and left wrist. During the week before admission he had a temperature as high as 102 F.; on several occasions he was nauseated and vomited; there was an intermittent dull aching over the precordium, and he had one profuse epistaxis.

At entry, the temperature was 100.4 F., and the pulse and respiratory rates were 80 and 24 respectively. The patient was well developed and well nourished, with a pale, hot, moist skin. The lips were cyanotic. The pharynx was injected. There were forceful pulsations of the vessels of the neck. The heart was enlarged and systolic and diastolic murmurs were heard over the base and the apex. There were peripheral signs of aortic regurgitation. Respiratory movements were rapid. Below the angle of the left scapula were dulness, increased whispered and voice sounds and a few medium moist râles. The right elbow, wrists, ankles and knees were red, hot, swollen and tender; the left shoulder was painful on motion.

On the day following admission, a pericardial friction rub was heard, which persisted during the two following days. The heart sounds were faintly heard and the pulse became of poor quality. The temperature reached 103 F.; the pulse rate increased to 140, and the respiratory rate mounted to 60. Sodium salicylate was given in doses of 150 grains (9.7 Gm.) daily, with no effect other than relief from the pain in the joints. Peripheral edema appeared and signs of pulmonary congestion, with the collection of rather large amounts of fluid at both bases of the lungs, were observed. The course was rapidly progressive, and death occurred five days after admission.

The roentgenogram of the chest, taken the day after entry, showed cloudy pulmonary fields (stasis). The total width of the heart shadow was 17.8 cm.; the inner diameter of the chest was 28 cm. The electrocardiogram, taken the same day, showed sino-auricular tachycardia, a pulse rate of 107, a PR interval of 0.2, T_2 diphasic and T_3 inverted. The blood, at the time of admission showed 16,500 leukocytes per cubic millimeter, 3,460,000 erythrocytes and 65 per cent hemoglobin. The differential leukocyte count revealed 82 per cent polymorphonuclears, 9 per cent lymphocytes and 9 per cent monocytes. A blood culture taken the day before death was sterile.

At autopsy, the right pleural cavity contained 500 cc., and the left, 200 cc., of thin yellow fluid. The pleural surfaces were smooth and glistening and were free from deposits of fibrin; no flecks of fibrin were found in the fluid. The lungs showed chronic passive congestion. The pericardial cavity was almost completely obliterated by fairly firm fibrous adhesions. Some fresh fibrin was deposited over the right auricle. The heart was markedly hypertrophied, weighing 760 gm. The myocardium showed atrophy of the muscular fibers. The cusps and leaflets of the mitral and aortic valves were opaque and slightly thickened; there was a single line of small, friable, yellowish-red vegetation along the free borders of these valves. The chordae tendineae were thickened and shortened. The lining of the endocardium of the right side of the heart was normal; the aorta was smooth and elastic.

The patient, with a rheumatic history of over ten years' duration, on admission to the hospital, showed polyarthritis, endocarditis, pericarditis

Synopsis of Fifteen Cases of Rheumatic Fever, Showing Pulmonary, Cardiac and Pleural Involvement

Case	Age and Sex	Rheumatic History: Polyarthritis, Age of Patient	Rheumatic History: Chorea, Age of Patient	Rheumatic History: Tonsillitis	Pulmonary Involvement	Cardiac Involvement: Pericarditis	Cardiac Involvement: Endocarditis	Cardiac Involvement: Electrocardiographic Abnormalities	Pleural Involvement
1	15 F	9 and 12	None	Rarely	Pleural pain in left axilla twelve days before entry; recurrence of pain persisted for five days before entry; dulness, distant breath sounds and friction rub in left axilla; roentgenogram showed fine mottling throughout both pulmonary fields; symptoms and signs disappeared by end of first week	None	Mitral stenosis and regurgitation; aortic regurgitation (developed during period of observation)	QRS complex slurred all leads, T waves flat in all leads*	Fibrinous pleurisy, left
2	50 M	28	None	Frequently	On entry, dulness, decreased breath sounds and friction rub in left axilla; a few crepitant râles at both bases posteriorly; roentgenogram showed patchy density in both middle and lower pulmonary fields; bronchopneumonia; signs of infiltration appeared over left base to persist for a week	Fibrinous	Mitral regurgitation	.....	Fibrinous pleurisy, left
3	41 F	38	None	.....	Signs of consolidation over right base, confirmed by roentgenogram, appeared one week after entry; friction rub at right base posteriorly one week after appearance of signs of consolidation; gradual disappearance of signs of consolidation during third week in hospital	Fibrinous	?	.....	Fibrinous pleurisy, right (jaundice—icteric index 75 on entry; gradual decrease)
4	33 M	None	None	Frequently	Severe pleural pain in right lower part of chest, subsiding for four days; signs of fluid with overlying friction rub at right base; roentgenogram showed fluid in lower third of right side of chest; following pleurocentesis, frank signs of consolidation persisted for five weeks	None	?	Partial heart block (PR interval, 0.2 to 0.28 sec.); T_3 diphasic or inverted*	Pleural effusion, right

5	28 M	13 and 19	None	Occasionally	Persistent cough for six days before entry; on entry, a few coarse râles at the left base, dulness, bronchovesicular breath sounds at the right base posteriorly and at the apex anteriorly; roentgenogram showed patchy density in both pulmonary fields, more marked on the right; signs unchanged until friction rub ten days later in the left axilla and effusion at the right base; fluid removed; signs of patchy consolidation and a small amount of fluid bilaterally persisted	Fibrinous	Mitral stenosis and regurgitation	Left ventricular predominance	Pleural effusion, bilateral
6	21 M	9	None	Rarely	On entry, a few fine râles throughout the chest; roentgenogram showed patchy lobular density at both bases; two weeks later, fluid at the right base; signs of consolidation at the right base followed and persisted for two weeks	Effusion (small)	Mitral stenosis and regurgitation	T_3 inverted*	Pleural effusion, right
7	25 M	18	None	Rarely	On entry, examination of the chest gave negative findings; four days later, consolidation of lower half of both lungs, followed by fluid at both bases; pleurocentesis and finally resorption after one month	Fibrinous	Mitral regurgitation	Deep Q_3, T waves inverted*	Pleural effusion, bilateral
8	16 M	11, 13, 14 and 15	None	.....	Pain in right side of chest, subsiding for two weeks; on entry, fluid at the right base; slight dulness, exaggerated breath sounds and crepitant râles at the right apex; pleurocentesis; disappearance of signs after five days	None	Mitral stenosis and regurgitation	Normal	Pleural effusion, right
9	23 M	6 and 13	None	.....	On entry, examination of the chest gave negative findings; roentgenogram showed slight cloudiness at left apex; two weeks later, fluid at the left base; pleurocentesis; consolidation in the left lower part of chest for two weeks	None	Aortic regurgitation	Paroxysmal tachycardia (auricular); partial heart block (PR interval, up to 0.44 sec.); left bundle branch block; left ventricular predominance; deep Q_3, QRS slurred all leads, T wave abnormalities*	Pleural effusion, left

* Digitalis not being given at the time of record.

Synopsis of Fifteen Cases of Rheumatic Fever, showing Pulmonary, Cardiac and Pleural Involvement—Continued

Case	Age and Sex	Rheumatic History: Poly-arthritis, Age of patient	Rheumatic History: Chorea, Age of Patient	Tonsillitis	Pulmonary Involvement	Cardiac Involvement: Pericarditis	Cardiac Involvement: Endocarditis	Cardiac Involvement: Electrocardiographic Abnormalities	Pleural Involvement
10	37 M	None	None	Occasionally	Bilateral pleural pain two days before entry; fluid at both bases overlying friction rubs in axillae; friction rub absent three days later, fluid persisted for five weeks	Fibrinous, followed by effusion (small)	Mitral regurgitation	Sino-auricular tachycardia; T_3 inverted*	Pleural effusion, bilateral
11	28 M	18	None	Occasionally	On entry, fluid at both bases, confirmed by roentgenogram; signs at right base absent after two weeks; after two weeks, signs of consolidation at right base reappeared to persist for another two weeks	Fibrinous, followed by effusion (moderately large)	Aortic regurgitation	Partial heart block (PR interval, 0.22 sec.); changes in T waves consistent with pericardial effusion	Pleural effusion, bilateral
12	15 F	14	None	Rarely	On entry, dulness, exaggerated breath sounds, a few râles over left apex and in left axilla; a small amount of fluid at both bases; all signs disappeared after three weeks	Effusion (moderate)	Mitral stenosis and regurgitation	Sino-auricular tachycardia; T_3 flat*	Pleural effusion, bilateral
13	35 M	None	None	Frequently	On entry, dulness and crepitant râles at angle of right scapula; a small amount of fluid at right base, disappeared after six days; three days later, a large amount of fluid at left base, resorbed after ten days	None	Mitral regurgitation	.....	Pleural effusion, bilateral
14	20 M	9, 12 and 17	12	Frequently	On entry, dulness, increased voice sounds and medium moist râles at angle of left scapula; roentgenogram showed cloudy pulmonary fields (stasis); rapid accumulation of fluid at both bases, with other signs of myocardial failure	Fibrinous (fibrous)	Mitral stenosis and regurgitation; aortic regurgitation	Sino-auricular tachycardia; T_2 diphasic, T_3 inverted	Pleural effusion, bilateral; myocardial failure (died, autopsy)
15	21 F	17	15 and 17	Frequently	On entry, scattered moist râles at both bases; flatness at the extreme bases; gradual disappearance of signs within a few days	None	Mitral stenosis and regurgitation	.....	Pleural effusion, bilateral; myocardial failure

* Digitalis not being given at the time of record.

and obvious myocardial damage. The course was that of a severe rheumatic infection with rapid myocardial failure leading to death. Autopsy revealed peripheral edema, bilateral hydrothorax, fibrous and fibrinous pericarditis, cardiac hypertrophy and active aortic and mitral endocarditis.

During the course of an exacerbation of rheumatic fever, pleural effusion may occur which is secondary to myocardial failure. With an acute exacerbation of the disease, the margin of reserve of the myocardial efficiency may be sufficiently impaired, either as a result of the myocardial involvement itself or because of the added burden of a more or less severe febrile disease, with or without the mechanical handicap due to valvular lesions, to lead to definite evidence of cardiac decompensation. Pleural effusion under these circumstances must not be confused with an effusion which is the direct result of rheumatic lesions of the pleural and underlying structures.

The more important clinical features of the cases studied are summarized in the table.

PULMONARY LESIONS

In reviewing the records of the thirteen patients who had pleural lesions as a feature of rheumatic fever, one is impressed by the frequency with which physical signs and roentgenologic evidence of involvement of the lung itself were observed. In each of the three cases of fibrinous pleurisy there was clinical evidence of pathologic changes in the lungs. Of the ten patients showing rheumatic pleurisy with effusion, five showed signs in the lung elsewhere than where pleural lesions were detected. In four patients, the signs of consolidation in the underlying lung were found after removal or absorption of the fluid. In two patients, pulmonary lesions were diagnosed prior to the appearance of signs pointing to pleural involvement. It seems significant that a pneumonic process was present in the patients in whom pleural lesions were encountered.

CARDIAC INVOLVEMENT

Endocardial lesions were diagnosed in eleven of the thirteen cases of rheumatic pleurisy. In nine cases, the process was confined to the mitral valve; two patients had aortic regurgitation, and in one case, which showed signs of mitral disease on entry, aortic regurgitation developed.

An associated pericarditis was diagnosed in eight of the thirteen cases; in four, the process was a fibrinous one; in the other four were signs of pericardial effusion subsequent to a fibrinous process which, however, never gave sufficient trouble to require removal.

There was no reason to suspect myocardial failure in the thirteen cases of rheumatic pleurisy. The clinical picture and the course of the illness in those patients who had effusions differed materially from

those of the two patients in whom there were bilateral effusions obviously resulting from myocardial failure.

The electrocardiogram gave abnormal deflections in nine of the ten cases studied. Paroxysmal auricular tachycardia, partial heart block and left bundle branch block were noted in a series of studies on one patient. The PR interval was prolonged beyond the normal limits in three other patients. Sino-auricular tachycardia occurred at times in three patients.

ONSET OF PLEURAL AND PULMONARY LESIONS

Polyarthritis preceded the symptoms referable to the thorax in eleven of the thirteen cases. In one instance, a sore throat was followed in two weeks by symptoms pointing to pleural and pulmonary lesions; joint symptoms did not appear until two weeks after the onset of the thoracic symptoms. In the other case, joint symptoms followed the onset of pericardial and pleural symptoms within six days.

In eight of the thirteen cases there was clinical evidence of acute pericarditis. The pleura was involved bilaterally in six cases. The right side alone was the site of a pathologic process in four instances, the left side alone in three instances. The onset of the pericardial lesion apparently preceded the pleural and pulmonary involvement in four of the eight cases. In two of these four cases there was at no time evidence of any active process localized in the left pleura, the pleural lesion being on the right side only. Involvement of the right side alone or primarily, followed by lesions in the left side and in the pericardium, occurred in six cases. The left lung and pleura were either the primary or the single site of an active process in two cases.

In this series of cases there seems to be a close association of pleural and pericardial lesions. However, there is little evidence that the pleural lesions were secondary to, or the result of, an extension from pericardial lesions. Howard [5] was of the opinion that the process in the pleura was probably an extension from the pericardium; similar conclusions have been drawn by subsequent observers. It would seem more probable that the pleural lesions are evidences of a more or less independent manifestation of the disease. The recognition of widespread vascular lesions in rheumatic fever has removed the necessity of relying on the explanation that pleural infection is an extension from the pericardium. The pleural lesions encountered in rheumatic fever may be due either to an extension from underlying pulmonary lesions or to processes simultaneously involving the pleural and subpleural layers, the cortico-pleuritis of Bezançon and Weil.[6]

5. Howard, R. P.: Rheumatism, in a System of Practical Medicine, by American Authors, edited by William Pepper, Philadelphia, Lea Bros. & Co., 1885, vol. 2, p. 19.

6. Bezançon, F., and Weil, M. P.: La cortico-pleurite rhumatismale, Ann. de méd. **19**:184 (Feb.) 1926.

PREVIOUS RHEUMATIC EPISODES

Of thirteen patients, three were seen in their first definite attack of rheumatic fever. The remaining ten patients had had from one to four previous attacks. In no patient was there any previous pulmonary and pleural involvement of a similar nature.

Colds in the head and tonsillitis were of common occurrence in five cases. In ten of the thirteen cases, the illness was preceded by an acute infection of the nasopharynx. In two other cases, examination of the pharynx and the tonsils revealed evidence of an acute infectious process.

CHARACTERISTICS OF PLEURAL FLUID

Seven specimens of pleural fluid from six patients were examined. These specimens were similar in most respects. Fluid was removed at intervals of two to fourteen days after the onset of symptoms and signs. Removal of the fluid was thought to be advisable from a therapeutic standpoint in but three instances. The most striking characteristics of the fluid were the hemorrhagic appearance and the readiness with which clot formation took place. The fluid from two patients was grossly bloody, while that from three other patients contained a sufficient number of erythrocytes to give it a pinkish-yellow color. Within ten or fifteen minutes after the withdrawal, the fluid in each of the seven cases formed a coagulum which enmeshed the cellular elements, leaving a clear, straw-colored fluid. This characteristic, repeatedly noted by numerous observers, has been ascribed to the high fibrin content. The cytologic studies were subject to variations too great to permit comparison. The leukocytes were not numerous, the counts varying between 600 and 3,750 per cubic millimeter.

Cultures of pleural fluid in each instance showed no growth. Guinea-pigs inoculated with specimens of fluid from three patients failed to show lesions characteristic of tuberculosis.

CLINICAL COURSE

In eleven of the thirteen cases, the illness began as polyarthritis; the onset of symptoms pointing to inclusion of the pericardium, lungs or pleura appeared during the second week of the illness except in three instances, in which the intervening period was but a few days. The onset of dyspnea, orthopnea, occasional mild cyanosis of the mucous membranes and pleural pain was sudden. Even in the cases in which pericardial lesions were absent or could be considered as negligible, the certainty of pulmonary lesions made the interpretation of the symptoms confusing. Dyspnea and orthopnea seemed out of all proportion to the extent of the process demonstrable. This disproportion between the severity of respiratory symptoms and the extent of pulmonary lesions has been commented on by Naish.[7] The severity of the dyspnea,

7. Naish, A. E.: The Rheumatic Lung, Lancet **2**:10 (July 7) 1928.

orthopnea and cyanosis was subject to marked alteration almost from hour to hour, without demonstrable changes in the physical findings.

The sputum was noted as being small in amount, tenacious and occasionally mucopurulent. In only one patient was the sputum grossly bloody, and this patient was subject to epistaxes during the period in which bloody sputum was observed.

The fever was of a continuous nature, with occasional slight remissions in twelve of the thirteen cases; in the other case, the temperature was irregularly intermittent. The temperature by mouth was 103 F. or higher at times, in seven cases. In no instance during the activity of the thoracic lesions did the temperature remain below 101 F. The maintenance of the temperature above 100 F. was subject to great variability; in one patient it remained above this point for twenty-nine days. The temperature approached a normal level with the subsidence of the thoracic lesions.

THERAPY WITH SALICYLATES

Sodium salicylate in doses ranging from 45 to 150 grains (2.9 to 9.7 Gm.) per day was administered with a similar amount of sodium bicarbonate. In no instance could it be said that the medication had any striking effect on the pleural or pulmonary lesions. This is in accord with the observations of Caussade and Tardieu [8] and of Grenet.[9] In one case therapy with salicylates was not instituted until after the subsidence of the pleural lesions—a period of approximately two weeks. No salicylates were given to another patient while she was in the hospital, and after ten days her temperature gradually fell, with disappearance of signs of pleural and pericardial lesions. The course of the processes in the lungs and pleura seemed not to differ essentially in those cases in which therapy with salicylates was withheld. Consistently the joint symptoms either disappeared or were lessened in severity following the institution of therapy with salicylates. However, with the onset of symptoms pointing to involvement of the lung and pleura there was a recurrence of the joint symptoms and signs, usually of a mild nature. The articular manifestations persisted, in spite of the therapy with salicylates, until effervescence of the pleuropulmonary lesions.

SUMMARY

Fifteen cases of rheumatic fever with pleural lesions were studied. Thirteen patients had rheumatic pleurisy; three, fibrinous pleurisy, and ten, pleurisy with effusion. Two patients had bilateral hydrothorax owing to myocardial failure during the acute stages of rheumatic fever.

8. Caussade, G., and Tardieu, A.: Classification clinique et thérapeutique des pneumopathies rhumatismales, Paris méd. **2**:157 (Aug. 23) 1930.

9. Grenet, H.: Les formes cliniques de la maladie rhumatismale (rhumatisme articulaire aigu et formes extra-articulaires), Monde méd., Paris **40**:809 (Oct.) 1930.

Involvement of the pleura was characterized by suddenness of onset and by dyspnea, orthopnea, mild cyanosis, pain (depending on the nature of the pleural lesion) and a febrile response varying in severity and duration.

Evidence pointed to concurrent pulmonary lesions in the patients who had true rheumatic pleurisy.

The pleural lesions were found to be independent of pericarditis and were related to underlying pulmonary processes.

The hemorrhagic nature and the readiness with which clot formation took place characterized the fluid of rheumatic pleurisy.

Polyarthritis was preceded by involvement of the pleura and lung in two instances.

Salicylates did not alter the course of the pleural and pulmonary lesions and, indeed, failed to relieve completely the articular symptoms in the presence of an extension of the rheumatic process to the pleura and lung.

Book Reviews

Physiological Effects of Radiant Energy. By Henry Laurens. Price, $6. Pp. 609. New York: The Chemical Catalog Company, Inc., 1933.

There has been so much discussion in the medical literature and quasimedical publications, often biased and without scientific foundation, that an authoritative book dealing with the effects of radiant energy on the body is to be welcomed. The vendor of the apparatus for radiant energy may insist, and even the user of various types of lamps may persuade himself, that there is a tremendous amount of virtue in artificial sunlight. There can be no question but that such is the truth; on the other hand, however, carbon arc lamps, ultraviolet lamps, quartz lamps or other types of lamps giving radiant energy are not the cure-alls that many believe them to be. It is therefore important that there be such a book as this which contains within it an unbiased, well balanced, scientific compilation of the use of radiant energy by one who has done a large amount of experimental work and who has made definite contributions to the subject.

Following the introductory sections there is a long chapter on the physics of radiant energy. Then follow chapters on the effects of radiant energy on the skin, wounds, the circulatory system, the blood, the metabolism, the body temperature, tuberculosis, bacteria and micro-organisms, toxins, antitoxins and so on. A bibliography of sixteen pages follows, succeeded by a complete index of authors and an equally complete index of subjects. The section on the effects of radiant energy on metabolism is most complete. Five chapters are devoted to this particular phase of radiant energy; naturally a not inconsiderable section has to do with the prevention and cure of rickets and the relationship of the ultraviolet rays to vitamin D.

This brief summary indicates the type of volume which Laurens has prepared so successfully. In the preface he states that he has compiled "a source book to which interested persons might resort to obtain information on the main work that has been done in this or that special field." With this purpose in mind the author naturally has not drawn conclusions. A criticism, which may or may not be valid, is that it does seem that the value of the book would be enhanced if conclusive statements were made by the author as one more fully qualified to elucidate contentious points than is the reader.

L'aérophagie et son traitement. By Félix Ramond, Physician to the Hôpital St.-Antoine, Paris, and Dimitresco-Popovici, Physician to the Hôpital Regina-Elisabeta, Bucharest. With the Collaboration of H. Dany. Paper. Price, 17 francs. Pp. 132, with 10 illustrations. Paris: Masson & Cie, 1933.

Les constipations. By M. Chiray, Physician to the Hôpital Bichat, Paris, and R. Stieffel, Consulting Physician at Plombières. With a historical note by Jean Vinchon, former Chief of Clinical Psychiatry, the Faculty of Medicine, Paris. Paper. Price, 20 francs. Pp. 157. Paris: Masson & Cie, 1933.

In 1923, Masson & Cie began to publish a series of short monographs under the name "Collection médecine et chirurgie pratiques." These monographs evidently have won a considerable degree of popularity, judged by their rate of growth, for up to the beginning of 1933 fifty-seven had appeared. In 1933 the two monographs with the titles mentioned have been printed, and one on the treatment of diabetes by Marcel Labbé is on the press.

Each monograph is short, inexpensive and, judging by the two latest samples, well printed on good paper. The group as a whole covers a wide range of subjects. A few of the volumes have been reviewed in *The Journal of the American*

Medical Association. They are well spoken of and appear to fulfil the purposes for which they were published, namely, to offer physicians a practical collection of booklets on subjects dealing with current medical and surgical knowledge. They are inexpensive, but are readable and easy to carry.

The monographs on aerophagy and constipation are merely additions to the series. The swallowing of air and its treatment are illustrated with roentgenographic charts and are disposed of in a sufficiently interesting fashion. There is an admirable historical account of constipation. The organic causes of chronic constipation are well discussed, so that the functional aspects of this habit are not unduly emphasized. On the whole, both monographs help to supplement the series and to make the collection of increasing interest to practitioners.

Clinical Aspects of the Electrocardiogram. By Harold E. B. Pardee, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College. Third edition. Price, $5.50. Pp. 295, with 74 illustrations. New York: Paul B. Hoeber, Inc., 1933.

The first edition of this book was published in 1924. It cost $4 and contained 222 pages with 56 illustrations. It was reviewed in the ARCHIVES (**34**:737 [Nov.] 1924) and in *The Journal of the American Medical Association* (**83**:1359 [Oct. 25] 1924). Both reviews spoke well of it, complimenting the author on his clarity of style and manner of presentation and predicting that this work would prove of practical value not only for reference but also in the clinic.

A second edition was published in 1928. By that time the volume had grown in size and was more expensive. It cost $5.50 and contained 242 pages with 60 illustrations. The second edition also was reviewed in the ARCHIVES (**43**:891 [June] 1929) and in *The Journal of the American Medical Association* (**91**:1181 [July 14] 1928). Both reviews again spoke cordially of the book and of the comprehensive manner in which the material had been put together. The second edition proved even more popular than the first and appeared to fill a considerable demand, as a reprinting was necessary in 1930.

The third edition has now appeared, a little longer in text and more profusely illustrated than its forbears, but otherwise conforming closely to their standards and form. There is little more to be said.

Dr. Pardee has brought his material up to date, changing or adding bits here and there in order to maintain his book at the level suggested by its title. In view of the enthusiastic way in which the preceding editions have been received, there is every reason for anticipating an equal success for the third. It is the kind of book that libraries, students, cardiologists and general practitioners will wish to own. It is recommended highly.

Methods and Problems of Medical Education. Twenty-First Series. Nursing Education and Schools of Nursing. Pp. 226. New York: Rockefeller Foundation, 1932.

This volume, the last of a series of twenty-one devoted to medical education, is on nursing education and schools of nursing. The study includes some of the outstanding nursing schools of the world. In the United States the schools that are used for examples of the advancement in nursing education are frequently connected with universities and in all respects are on the same level as the other departments of the university. This indicates that requirements for entrance to schools of nursing are more stringent than formerly and emphasizes the necessity for young women with good educational and cultural backgrounds. The ratio of theory to practice is another important factor. The advanced schools are constantly experimenting on the amount of theory that should be given with clinical experience. One of the accepted ratios is that seven hours of practical experience for fifteen weeks count as one lecture hour. Fifteen per cent of the course is devoted to theory. This is interesting, as at present there is considerable comment about the amount of theory a nurse should have.

Nursing schools in foreign countries present much the same problems as those in the United States. However, in many of the countries the most outstanding schools are based on the American plan of nursing education. Since standards of nursing education are changing along with standards of education in other fields, there is a question as to whether the present system of training the nurse is the wisest. Unquestionably, as more is required and expected of a nurse today than formerly, one who wishes to qualify as a nurse must recognize the necessity for intensive study and a conscientious desire to give service.

Der Weg zur rationellen Therapie. Edited by Prof. Dr. A. Fraenkel, Heidelberg. Price, 10.80 marks. Pp. 183. Leipzig: Georg Thieme, 1933.

This book consists of reports of lectures given at Heidelberg in August, 1932, which correspond to what in America would be called a postgraduate course, the purpose of which is to discuss "the exact use of specific therapeutic agents on the basis of their pharmacologic action." Mercury, digitalis, thyroxine, arsphenamine, the vitamins and antianemic liver preparations receive consideration by such authorities as Straub, Sachs, György, Gänzlen and others. The summaries bring the subjects up to date in an adequate manner, and the bibliographies attached to some of the articles are especially useful.

Radiologic Maxims. By Harold Swanberg. Price, $1.50. Pp. 127. Quincy, Ill.: Radiological Review Publishing Company, 1932.

This small book represents a collection of certain radiologic maxims which have appeared in the last six years in the *Radiological Review* and *the Chicago Medical Recorder*. There are additional quotations which have to do with various radiologic subjects. Necessarily the maxims are dogmatic, succinct and in some instances questionable. Apparently these maxims are written for the radiologist primarily, because the claims that they make for the x-rays in diagnosis and in therapy are a bit too comprehensive for any one but a rabid enthusiast to swallow whole.